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Canine Diabetic Ketosis-Ketoacidosis: A Retrospective Study of 23 Cases (1997-2013)

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Κετοτικός-Κετοξεωτικός Σακχαρώδης Διαβήτης στο Σκύλο: Αναδρομική Μελέτη σε 23 Περιστατικά (1997-2013)

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ABSTRACT. The purpose of this retrospective study was to describe the historical and clinical findings, the clinicopathological abnormalities, the occurrence and nature of concurrent diseases, the treatment and outcome of 23 dogs with diabetic ketosis-ketoacidosis (DK-DKA). Inclusion criteria consisted of the presence of clinical signs suggestive of diabetes mellitus (DM) along with persistent hyperglycemia, glycosuria and ketonuria during the first 24 hours of hospitalization. In nineteen dogs (83%) DM had not been previously diagnosed. Common presenting complaints were polyuria/polydipsia (100%), partial or complete loss of appetite (87%), depression (87%), vomiting (65 %) and weight loss (30 %). The most frequent physical examination findings included dehydration (61%), depression (61%), hypotrichosis-alopecia (39%), palpable cranial abdominal organomegaly (26%), pendulous abdomen (26%), lesions compatible with superficial pyoderma (17%), thin and hypotonic abdominal skin (17%), and hypothermia (17%). The most important clinicopathological abnormalities, apart from hyperglycemia, glucosuria, and ketonuria, included anemia (48%), leukocytosis (39%), increased activities of alkaline phosphatase (100%), lipase (56%) and alanine aminotransferase (52%), hypertriglyceridemia (90%) and hypercholesterolemia (84%). Also, 12 dogs demonstrated hypokalemia on admission or during hospitalization. A concurrent disease was identified in 74% of the cases while 26% had two or more comorbidities. The latter included pancreatitis (30%), urinary tract infections (17%), superficial pyoderma (17%), urolithiasis (13%) and hyperadrenocorticism (13%). Twenty two dogs were treated with short-acting insulin (regular or lispro) and one with intermediate-acting (lente) insulin, whereas intravenous fluid therapy was instituted in 78% of them with potassium and phosphorus supplementation in 65% and 9%, respectively. Seventeen (81%) dogs survived to be discharged, three (13%) died during hospitalization, one (4%) was euthanized and on two (9%) occasions owners declined hospitalization after the first 24 hours due to financial constraints or a poor prognosis. Mean duration of hospitalization for the survivors was 5.7 ± 2.4 days, mean time to resolution of ketonuria was 4.2 ± 1.9 days and median time of rapid-acting insulin administration was 4 days (range 2-8 days).

Keywords: diabetes mellitus; dog; ketosis; ketoacidosis; pancreatitis

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ΠΕΡΙΛΗΨΗ. Σκοπός της αναδρομικής αυτής μελέτης ήταν η περιγραφή του ιστορικού, της κλινικής εικόνας, των εργαστηριακών ευρημάτων, των συνυπαρχόντων νοσημάτων, της θεραπείας και της έκβασης 23 σκύλων με κετοτικό-κετοξεωτικό σακχαρώδη διαβήτη (ΚΣΔ-ΚΟΣΔ). Τα κριτήρια συμμετοχής στη μελέτη ήταν η συμβατή με το σακχαρώδη διαβήτη συμπτωματολογία, καθώς και η διαπίστωση υπεργλυκαιμίας, γλυκοζουρίας και κετονουρίας στη διάρκεια νοσηλείας που διήρκησε τουλάχιστον 24 ώρες. Σε δεκαεννέα σκύλους (83%) η διάγνωση του σακχαρώδη διαβήτη έγινε για πρώτη φορά όταν αυτοί προσκομίσθηκαν με ΚΣΔ-ΚΟΣΔ. Τα πιο συχνά συμπτώματα από το ιστορικό ήταν η πολουρία-πολυδιψία (100%), η επιλεκτική όρεξη ή η ανορεξία (87%), η κατάπτωση (87%), οι έμετοι (65%) και η απώλεια σωματικού βάρους (30%). Τα συχνότερα κλινικά ευρήματα που οφείλονταν στο σακχαρώδη διαβήτη, στον ΚΣΔ-ΚΟΣΔ ή τα συνυπάρχοντα νοσήματα ήταν η αφυδάτωση (61%), η κατάπτωση (61%), η υποτρίχωση-αλωπεκία (39%), η ψηλαφησίμη οργανομεγαλία στην πρόσθια κοιλία (26%), η κρεμάμενη κοιλία (26%), οι συμβατές με την επιπολής βακτηριακή δερματίτιδα αλλοιώσεις (17%), το λεπτό και υποτονικό δέρμα στην κάτω κοιλιακή χώρα (17%), και η υποθερμία (17%). Εκτός από το συνδυασμό υπεργλυκαιμίας, γλυκοζουρίας και κετονουρίας, συχνές εργαστηριακές διαταραχές ήταν η αναιμία (48%), η λευκοκυττάρωση (39%), η αύξηση της δραστηριότητας της αλκαλικής φωσφατάσης (100%), της λιπάσης (56%) και της αλανινοαμινοτρανσφεράσης (52%), η υπερτριγλυκεριδαίμια (90%) και η υπερχολοστερολαιμία (84%). Επιπλέον, σε 12 σκύλους διαπιστώθηκε υποκαλιαιμία κατά την προσκόμιση ή στη διάρκεια της νοσηλείας. Συνυπάρχουσες παθολογικές καταστάσεις διαγνώσθηκαν στο 74% των σκύλων, ενώ στο 26% διαπιστώθηκαν περισσότερες από μια, με την παγκρεατίτιδα (30%), τις βακτηριακές ουρολοιμώξεις (17%), την επιπολής βακτηριακή δερματίτιδα (17%), την ουρολιθίαση (17%) και τον υπερφλοιοεπινεφριδισμό (13%) να είναι οι συχνότερες από αυτές. Σε 22 σκύλους χορηγήθηκε ινσουλίνη βραχείας δράσης (κρυσταλλική ή lispro) και σε ένα ινσουλίνη ενδιάμεσης διάρκειας δράσης (lente). Παράλληλα, κρυσταλλοειδή διαλύματα, κάλιο και φώσφορος χορηγήθηκαν ενδοφλέβια σε 78,3%, 65,2% και 8,7% των σκύλων της μελέτης, αντίστοιχα. Σε 17 σκύλους η έκβαση ήταν ευνοϊκή (81%), τρεις (13%) πέθαναν κατά τη διάρκεια της νοσηλείας, σε ένα (4%) έγινε ευθανασία, ενώ σε δύο (9%) περιπτώσεις οι ιδιοκτήτες αρνήθηκαν τη νοσηλεία του ζώου μετά το πρώτο εικοσιτετράωρο για οικονομικούς λόγους ή λόγω της δυσμενούς πρόγνωσης. Αναφορικά με τους σκύλους που ανταποκρίθηκαν στη θεραπεία, η μέση διάρκεια νοσηλείας ήταν $5,7 \pm 2,4$ ημέρες, ο μέσος χρόνος για να εξαφανιστεί η κετονουρία και η διάμεση τιμή του χρόνου που διήρκησε η θεραπεία με ινσουλίνης βραχείας δράσης ήταν $4,2 \pm 1,9$ και 4 (εύρος: 2-8) ημέρες, αντίστοιχα.

Λέξεις ευρετηρίασης: κετοξέωση, κέτωση, παγκρεατίτιδα, σακχαρώδης διαβήτης, σκύλος

INTRODUCTION

Diabetic ketosis-ketoacidosis DK-DKA is a severe and potentially fatal metabolic complication of uncontrolled diabetes mellitus (DM). An absolute or relative insulin deficiency due to decreased secretion and/or increased peripheral resistance is pivotal to the pathogenesis of DK-DKA. Increases in counterregulatory hormone concentration, predominately glucagon, in association with coexisting diseases, further contribute to the development of the syndrome (O'Brien, 2009). The diagnosis of DK-DKA is based on the presence of hyperglycemia, glycosuria, ketonemia and/or ketonuria with or without metabolic acidosis (Di Tomasso et al., 2009; Hess, 2013). Only a few studies have been published addressing the outcome of dogs with DK-DKA (Hume et al., 2006; Sears et al., 2011).

The purpose of this retrospective study was to describe the historical, clinical and clinicopathologic abnormalities, concurrent diseases, treatment and outcome in a series of 23 diabetic dogs with ketonuria.

MATERIALS AND METHODS

A manual search of the medical records of the Companion Animal Clinic, School of Veterinary Medicine, Aristotle University of Thessaloniki, between January 1997 and March 2013, for dogs with a diagnosis of DK-DKA was conducted. Inclusion criteria were the presence of hyperglycemia (blood glucose ≥ 250 mg/dl), glycosuria (urinary glucose > negative) and ketonuria (urinary acetate acid (AcAc) > negative) during the first 24 hours of hospitalization. Animals were excluded if complete medical records were not available and/or if they were not hospitalized for at least 24 hours.

Information on signalment, medical history, physical examination and clinicopathological findings, aerobic bacterial urine culture, imaging findings, concurrent diseases, insulin treatment (type, route and duration of administration, complications), duration of hospitalization, time to resolution of ketonuria (time from admission to a negative urinary

AcAc), and final outcome (survival or death/euthanasia) were recorded.

Serum potassium concentrations on admission as well as the lowest potassium concentration measured during hospitalization were recorded. Serum sodium concentrations are reported as measured sodium [Na_m] and as sodium values corrected for hyperglycemia according to the formula: Sodium corrected [Na_c] = $1.6 \times ([\text{measured glucose} - \text{normal glucose}]/100) + [Na_m]$, where 100 mg/dl was used as the normal glucose value (Koenig, 2013). Effective serum osmolality (OsmE) was calculated with the formula: OsmE: $2[Na_m] + [\text{glucose}]/18$. Hyperosmolality was defined as OsmE >310 mOsm/L and severe hyperosmolality as OsmE >330 mOsm/L (Schermerhorn and Barr, 2006). Blood b-hydroxybutyric acid (BOH) was measured with a validated hand held portable meter (Precision Xtra, Abbot Diabetes Care Inc) and concentrations >3.5 mmol/L were considered consistent with ketoacidosis when metabolic acidosis was also documented (Di Tommaso et al., 2013). Animals were considered to have metabolic acidosis when pH and bicarbonate concentration was <7.3 and <15 mmol/L respectively (O'Brien, 2010).

Continuous variables were assessed for normality by visual inspection of scatterplots and the Shapiro-Wilks test; normally distributed variables are presented as mean \pm standard deviation whereas non-normally distributed variables as median and range (minimum-maximum). Prevalences were rounded to whole numbers due to the small number of cases. For simplicity, complete blood count (CBC) and serum biochemistry results on admission are described as median and range regardless of normality.

RESULTS

A total of 29 dogs were retrieved with a diagnosis of DK-DKA, but four were excluded due to incomplete medical records and two because they had not been hospitalized for at least 24 hours, both due to financial concerns. None of the animals that were hospitalized less than 24 hours died. Therefore, 23 dogs were included in the study.

Signalment

The study population included six Poodles (26%), five mixed-breed dogs (22%), three Yorkshire terriers (13%), two Maltese (9%) and one (4%) dog from each of the following breeds: Doberman pinscher, Pomeranian, Siberian husky, Pekingese, West Highland White terrier, Cavalier King Charles Spaniel and Beaucheron. Mean age at the time of admission was 9 ± 1.5 years. Thirteen dogs (56%) were intact females, three (13%) neutered females and seven (30%) were intact males.

Historical information and physical examination findings

Nineteen (83%) dogs with DK-DKA had not a previous diagnosis of DM, whereas for the remaining four (17%) the median time from DM diagnosis to the development of DK-DKA was 65 days (range: 1-180 days). Insulin had been previously administered in three of these dogs, but type, dosage and duration of treatment were not available for review. The most common presenting complaints were PU/PD (23/23; 100%), partial or complete anorexia (20/23; 87%), depression (20/23; 87%) vomiting (15/23; 65%), and weight loss, while in 8/20 (40%) dogs that presented with partial or complete anorexia polyphagia preceded for various periods of time. Median duration of symptoms was 60 days (range: 2-180 days). Historical information are presented in table 1.

Physical examination findings are provided in table 2. Eight (35%) dogs were overweight, nine (39%) had an optimal body condition and six (26%) were underweight. Moderate to severe dehydration was detected in fourteen animals (61%), while the remaining nine (39%) were considered adequately hydrated. Other common clinical findings included depression (14/23; 61%), hypotrichosis-alopecia (9/23; 39%), cranial abdominal organomegaly (6/23; 26%) and a pendulous abdomen (6/23; 26%).

Clinicopathologic findings

Complete blood counts (CBC) and serum biochemistry results on admission from all dogs were

Table 1 Historical information on admission of 23 dogs with diabetic ketosis-ketoacidosis

| Historical information | No of dogs (%) |
|---------------------------|----------------|
| Polyuria/polydipsia | 23/23 (100%) |
| Partial/complete anorexia | 20/23 (87%) |
| Depression | 20/23 (87%) |
| Vomiting | 15/23 (65.2%) |
| Weight loss | 7/23 (30.4%) |
| Weakness | 4/23 (17.4%) |
| Skin lesions | 3/23 (13%) |
| Regurgitation | 2/23 (8.7%) |
| Melena | 2/23 (8.7%) |
| Pendulous abdomen | 2/23 (8.7%) |
| Hematochezia | 1/23 (4.3%) |
| Diarrhea | 1/23 (4.3%) |
| Hematuria | 1/23 (4.3%) |
| Dyspnea | 1/23 (4.3%) |

available for review and their median values and ranges are presented in table 3. Anemia and leukocytosis were identified in 11/23 (48%) and 9/23 (39%) dogs respectively. Hyperglycemia was documented in 22/23 (96%) cases; the only exception was a dog that had received insulin shortly before admission, but demonstrated hyperglycemia during the following 24 hours. Additional common serum biochemistry abnormalities included increased alkaline phosphatase (ALP) activity (20/20-100%), hypertriglyceridemia (17/19-89%), hypercholesterolemia (16/19-84%), and alanine aminotransferase (ALT) (11/21-52%) activities. Also, pancreatic lipase immunoreactivity (cPLI) was above reference range (≥ 400 $\mu\text{g/L}$) and thus consistent with pancreatitis in 6 out of the 7 animals that was measured, while Snap cPL (Canine Pancreatic Lipase Test kit, IDEXX) was abnormal in 5 additional cases.

Potassium concentration on admission was measured in 22 dogs and was found to be low or high in 8 (36%) and 2 (9%) cases, respectively. Potassium measurements were repeated during hospitalization

in nine dogs with normal or increased concentrations on admission, revealing hypokalemia in four of them, besides the intravenous (IV) administration of potassium chloride in 3/4 dogs. The median potassium values for these 9 dogs before and during treatment were 5 mmol/l (range: 4-6.6 mmol/l) and 3.8 mmol/L (range: 2.1-6.1 mmol/l), respectively. Overall, hypokalemia was documented in 12/22 dogs. Hyponatremia was present in 17/21 (81%) dogs on admission based on $[\text{Na}_m]$ concentrations; however, $[\text{Na}_c]$ was decreased in 13/21 (62%) dogs, within reference range in 7/21 (33%) and increased in 1/21 (5%). OsmE was >310 mOsm/L and >330 mOsm/L in 5/21 (24%) and 1/21 (5%) dogs, respectively. BOH concentration was measured in 11 dogs; the median value was 4.1 mmol/l (range: 0.9-7.6 mmol/l) and the concentration was in excess of 3.5 mmol/l in 8/11 (73%) of them. Blood gas analysis was done in 9 dogs to show metabolic acidosis in 4/9 (44%) of them. Therefore, from the nine animals with a known metabolic status DK and DKA was diagnosed in five and four animals, respectively.

Urine specific gravity (USG) was >1030 and 1010-1029 in 11/23 (48%) and in 12/23 (52%) dogs, respectively. Besides glucosuria and ketonuria that had to be present in all dogs, glomerular proteinuria was detected in 16/23 (67%) based upon positive Heller's reaction and inactive urine sediment. Urine cultures were performed in 15 dogs and were positive in four (27%) of them; *Escherichia coli* was isolated in two cases while *Enterococcus* spp. and *Staphylococcus* spp. in one dog, each. Active urine sediment was present in two of these dogs, while only one exhibited symptoms suggestive of lower urinary tract disease.

Imaging studies

Abdominal radiographs were performed in 15 cases. Hepatomegaly was identified in 8 (53%) dogs; other findings included urinary bladder calculi and renal calcification in three (20%) and one (7%) dog, respectively. Abdominal ultrasonography was conducted in 18 dogs and the most common finding was hepatomegaly (12/18; 67%). Adrenal enlargement (3/18; 17%), hyperechoic pancreas (3/18; 17%) and

urinary bladder calculi (3/18; 17%) were additional abnormalities.

Concurrent diseases

In seventeen dogs (74%) a disease other than DK-DKA was also documented and in six (26%) animals more than one and up to three concurrent conditions were observed. A diagnosis of acute pancreatitis was established in 7 cases (30%) based on a combination of compatible clinical signs, abdominal ultrasound, cPLI and Snap cPL results and necropsy findings. Animals with a positive Snap cPL and without positive cPLI or compatible necropsy findings were not considered to have pancreatitis. Hyperadrenocorticism (HAC) had been diagnosed prior to DK-DKA in three cases with adrenal function tests (ACTH stimulation test and low dose dexamethasone suppression test). The remaining concurrent diseases included urinary tract infection (UTI; 4/23; 17%), superficial pyoderma (4/23; 17%), urolithiasis (3/23; 13%), mammary gland neoplasia (2/23; 9%), leptospirosis (1/23; 4%), septic laryngeal granuloma

Table 2 Clinical examination findings on admission of 23 dogs with diabetic ketosis-ketoacidosis.

| Physical examination findings | No of dogs (%) |
|--------------------------------|----------------|
| Depression | 14/23 (60.9%) |
| Dehydration | 14/23 (60.9%) |
| Hypotrichosis-alopecia | 9/23 (39.1%) |
| Cranial abdominal organomegaly | 6/23 (26.1%) |
| Pendulous abdomen | 6/23 (26.1%) |
| Superficial pyoderma | 4/23 (17.4%) |
| Thin/hypotonic abdominal skin | 4/23 (17.4%) |
| Hypothermia | 4/23 (17.4%) |
| Peripheral lymphadenomegaly | 3/23 (13%) |
| Abdominal pain | 2/23 (8.7%) |
| Dyspnea | 2/23 (8.7%) |
| Mucosal pallor | 2/23 (8.7%) |
| Jaundice | 2/23 (8.7%) |
| Ascites | 1/23 (4.3%) |
| Fever | 1/23 (4.3%) |

Table 3 Complete blood count and serum biochemistry results on admission of 23 dogs with diabetic ketosis-ketoacidosis

| Variable | N | Median | Range | Above RR | Normal value | Below RR | RR |
|----------------------------------|----|---------|--------------------|-------------|-----------------|-------------|-----------------|
| Hematocrit (%) | 23 | 37.1 | 23.2-52.1 | 0 | 12 | 11 | 37-55 |
| WBC (μL^{-1}) | 23 | 15,440 | 5,840-44,700 | 9 | 13 | 1 | 6,000-17,000 |
| Platelets (μL^{-1}) | 23 | 571,500 | 10,350- 978,000 | 13 | 9 | 1 | 200,000-500,000 |
| BUN (mg/dl) | 22 | 31.5 | 8-179 | 6 | 13 | 3 | 10-38 |
| Creatinine (mg/dl) | 22 | 0.9 | 0.2-6.7 | 4 | 13 | 5 | 0.7-1.3 |
| Glucose (mg/dl) | 23 | 452 | 118-621 | 22 | 1 | 0 | 65-118 |
| Cholesterol (mg/dl) | 19 | 403 | 202-850 | 16 | 3 | 0 | 125-296 |
| Triglycerides (mg/dl) | 19 | 288 | 39-2,000 | 17 | 2 | 0 | 24-102 |
| Tbil (mg/dl) | 12 | 0.6 | 0.4-10.3 | 4 | 8 | 0 | 0.2-0.6 |
| ALP (U/L) | 20 | 1,109 | 256-8,520 | 20 | 0 | 0 | 32-149 |
| ALT (U/L) | 21 | 64 | 14-450 | 11 | 10 | 0 | 18-62 |
| Lipase (U/L) | 9 | 251 | 25-2,081 | 5 | 4 | 0 | 5-32 |
| Calcium (mg/dl) | 18 | 8.2 | 6.9-11.5 | 1 | 6 | 11 | 8.6-10.9 |
| IP (mg/dl) | 19 | 4.7 | 2-10.8 | 1 | 13 | 5 | 2.2-6 |
| Potassium (mEq/L) | 22 | 4 | 2.8-6.6 | 8 | 12 | 2 | 3.7-5.9 |
| Na _m (mEq/L) | 21 | 139.9 | 124-156 | 17 | 4 | 0 | 144-158 |
| Na _c (mEq/L) | 21 | 142.7 | 126.8-159.3 | 13 | 7 | 1 | 144-158 |
| OsmE (mOsm/L) | 21 | 298.5 | 263-335 | 5 | 16 | 0 | <310 |
| BOH (mmol/l) | 11 | 4.1 | 0.9-7.6 | 8 | 3 | 0 | ≤2.0 |
| pH | 9 | 7.31 | 7.07-7.49 | 4 | 5 | 0 | >7.3 |
| Bicarbonate (mmol/l) | 9 | 14.3 | 6.3-16.8 | 4 | 5 | 0 | >15 |

N: number of dogs, RR: reference range, WBC: white blood cells, BUN: blood urea nitrogen, Tbil: total bilirubin, ALP: alkaline phosphatase, ALT: alaninoaminotransferase, IP: inorganic phosphorus, Nam: sodium measured, Nac: sodium calculated, OsmE: effective osmolality, BOH: b-hydroxybutiric acid.

(1/23; 4%), aspiration pneumonia (1/23; 4%), pyometra (1/23; 4%), prostatic abscess (1/23; 4%), hypothyroidism (1/23; 4%), pulmonary thromboembolism (PTE) (1/23; 4%) and acute renal failure (1/23; 4%).

Treatment and outcome

The treatment was individualized according to the clinical severity, the identification of concurrent diseases, the response of the dog, and the preference of the attending clinician.

IV fluids were administered to 18/23 (78%) dogs. Normal saline (NS 0.9%; sodium chloride 0.9%) was used in all instances; additionally, dextrose containing fluids (NS 0.45% plus dextrose 2.5% or dextrose 5%) were administered based on serial blood glucose measurements in 11/23 dogs (48%). Potassium and phosphorus supplementation of the IV fluids was practiced in 15/23 (65%) and 2/23 (9%) dogs, respectively and their infusion rates were adjusted on the basis of serial serum electrolyte measurements.

Protocols for the management of DK-DKA were according to the literature. IV insulin was administered as a constant rate infusion after adding 2.2 U/kg of either regular or lispro insulin in 250 ml of NS 0.9%. Initial rate was 10 ml/hr and adjustments were made depending on serial glucose measurements (Macintire, 1993; Sears et al., 2012). Insulin was administered intramuscularly (IM) at an initial dose of 0.2 U/Kg initially and then at 0.1 U/Kg hourly. Dose adjustments were made based on serial blood glucose measurements. In responsive animals insulin could be switched to subcutaneous (SC) administration. Healthy ketotic dogs were treated with SC regular insulin every 6-8 hours. Glucose measurements were conducted on all instances hourly for animals receiving insulin IM and every two hours on all other occasions (Feldman and Nelson 2004). Nineteen animals (83%) were treated with regular insulin (Humulin-R®, Pharmasern Lilly), 2/23 (9%) with lispro (Humalog®, Eli Lilly Nederlands BV). In one case (4.3%) regular insulin was initially used followed by lispro and in one dog (4%) treatment included only lente insulin (Caninsulin®, Intervet). Insulin preparations were administered IM in 9/23 (39%), SC in 9/23 (39%) and IV in 2/23 (9%) dogs.

In two cases (9%), IM insulin administration was followed by the IV protocol due to poor responsiveness, while in one dog (4%) IM was followed by SC insulin. For the five animals with confirmed DK two were treated with SC insulin administration while the IM, IM followed by SC and IV protocol was employed in one dog each. DKA dogs were treated with the IM, IM followed by SC and IV protocol (one animal each), while in one dog insulin was administered IM initially and due to poor responsiveness the IV protocol was employed. Additional treatments, depended on the severity of the symptoms and the nature of concurrent diseases and were administered in 17/23 (74%) dogs (Table 4).

Seventeen dogs (17/21; 81%) survived to be discharged from the hospital. Mean duration of hospitalization for survivors was 5.7 ± 2.4 days. Three animals (13%) died and one was euthanized (4%) after 5.5 ± 1.9 days. In two more occasions (9%) owners declined hospitalization after the first 24 hours due to financial concerns or poor prognosis and were lost to follow up. Overall hospitalization time was 6.1 ± 1.9 days. Median duration of rapid-acting (regular, lispro) insulin administration for survivors was 4 days (range 2-8 days) and the mean time from the first administration to resolution of ketonuria was 4.2 ± 1.9 days. For the two dogs that received lispro alone time to resolution of ketonuria were 3 and 5 days. Accordingly, mean time for those treated with regular was 4 ± 1.9 days. The animal that received a combination of the above insulin types did not survive to be discharged. For the dogs with confirmed metabolic acidosis, three died and one survived to be discharged after six days of hospitalization. Time to resolution of ketonuria and duration of rapid acting insulin administration was 5 days. All the non-survivors DKA dogs had a diagnosis of acute pancreatitis along with more than one concurrent disease. All five animals with normal blood gas analysis on admission survived to be discharged with a median time of hospitalization, urine ketone remission and duration of rapid acting insulin administration 6 (range 4-9), 5 (range 2-6) and 4 (range 2-8) days respectively. Four animals (17%) developed asymptomatic hypoglycemia during hospitalization and one more (4%) loss of consciousness and decerebrate rigidity due to

Table 4 Treatments in addition to fluids, electrolytes and insulin in 23 dogs with diabetic ketosis-ketoacidosis

| Treatment | N° of dogs | Percentage |
|---|------------|------------|
| <i>Antimicrobials</i> | | |
| Enrofloxacin (Baytril [®] , Bayer) | 8 | 34.8% |
| Ampicillin (Pentrexyl [®] , Bristol-Myers Squibb; Begalin [®] , Pfizer) | 6 | 26.1% |
| Cefuroxime (Zinacel [®] , GlaxoSmithKline) | 2 | 8.7% |
| Marbofloxacin (Marbocyl [®] , Vetoquinol) | 2 | 8.7% |
| <i>Antiemetics, H₂ blockers and gastric protectants</i> | | |
| Metoclopramide (Primperan [®] , Sanofi-Aventis) | 8 | 34.8% |
| Ranitidine (Zantac, GlaxoSmithKline) | 6 | 26.1% |
| Maropitant citrate (Cerenia [®] , Pfizer) | 4 | 17.4% |
| Sucralfate (Peptonorm, Uni-Pharma) | 3 | 13% |
| Cimetidine (Tagamet, Vianex) | 2 | 8.7% |
| Ondasetron (Zofron [®] , GlaxoSmithKline) | 1 | 4.3% |
| <i>Miscellaneous</i> | | |
| Butorphanol (Butador [®] , Pfizer) | 2 | 8.7% |
| Tramadol (Tramal [®] , Vianex) | 2 | 8.7% |
| Ursodeoxycholic acid (Ursofalk [®] , Galenika) | 1 | 4.3% |
| Heparin (Heparin [®] , LEO Pharmaceuticals) | 1 | 4.3% |

presumed cerebral edema during the second day of hospitalization. The latter dog was treated with regular insulin administered IM at an initial dose of 0.2U/kg followed by hourly injections of 0.1 U/kg. Glucose was measured hourly.

Discussion

In both human and veterinary medicine, common precipitating factors for the development of DK-DKA include undiagnosed DM, concurrent disease(s), inadequate control of blood glucose concentrations in previously diagnosed diabetics, or a combination thereof (Feldman and Nelson, 2004; Nyenwe and Kitabchi, 2011). In the vast majority of our cases, DK-DKA was diagnosed concurrently with DM besides the relatively long duration of symptoms (60 days; range: 2-180 days), indicating that failure of the owners to recognize the clinical signs of uncomplicated DM and to timely ask for

veterinary help was the reason for the large percentage (83%) of dogs diagnosed simultaneously with DK-DKA and DM (Feldman and Nelson, 2004). Only four dogs were previously diagnosed diabetics and three of them were treated with insulin when DK-DKA emerged but due to the lack of information on the type, dose and duration of insulin administration and blood glucose concentrations we were unable to assess if DK-DKA developed due to poor glycemic control and/or due to the presence of concurrent disease.

The historical information and physical examination findings in the present series are similar to those previously reported, with the exception of hydration status. The prevalence of dehydrated dogs in our study population is considerably lower compared to previous investigations (Chastain and Nichols, 1981; Macintire, 1993; Hume et al., 2006). In these studies, dehydration and/or metabolic acido-

sis were among the inclusion criteria, thus, entailing the enrollment of animals with more severe illness (i.e. dogs with DKA). The clinical severity may vary greatly in DK-DKA, ranging from ketonuric, otherwise healthy, to moribund dogs, and is largely dependent on the development and severity of metabolic acidosis, the presence and nature of concurrent disease(s) and the duration of illness (Stojanovic and Ihle, 2011). In this study, acid-base status was investigated in relatively few dogs (9/23; 39%) and metabolic acidosis that was confirmed in four of them was not an inclusion criterion, thus allowing the inclusion of healthy ketotic animals, providing a plausible explanation for the relatively high percentage of well hydrated dogs.

Leukocytosis was observed in nine (39%) of the dogs and is considered a common laboratory finding in DK-DKA, occurring in up to 59% of cases. Although it has been associated with prolongation of hospitalization time, it does not seem to affect survival rate (Chastain and Nichols, 1981; Macintire, 1993; Hume et al., 2006). Leukocytosis may be either stress-induced or due to the presence of a concurrent inflammatory process, with the latter being more common when white blood cell counts are in excess of 30,000/ μ l with or without a left shift and when toxic neutrophil changes are present (Feldman and Nelson, 2004). In this study, underlying diseases in dogs with leukocytosis included acute pancreatitis alone (1/9; 11%), acute pancreatitis and prostatic abscess, UTI or aspiration pneumonia (3/9; 33%), PTE (1/9; 11%), and UTI (1/9; 11%), while none was found in 3/9 (33%) cases. Interestingly, in a study of children with DK-DKA, leukocytosis was significantly correlated with arterial blood pH and bicarbonate concentration but not with the presence of an inflammatory disease, leading to the conclusion that most likely it reflects the severity of the disease rather than the presence of inflammation (Flood and Chiang, 2001).

Increases in serum ALP and ALT activities along with hypertriglyceridemia and hypercholesterolemia were common biochemical abnormalities in this series. Increased liver enzyme activity secondary to hypoxia, hypovolemia, concurrent disease(s) or

lipemia are frequently reported in DK-DKA (Kerl, 2001a). DM, is a well known cause of lipid metabolism derangement in dogs and it is especially correlated with increased triglyceride concentration. Caution must be exercised in the interpretation of biochemical results in patients with moderate to severe lipemia, since it may interfere with the measurement of certain biochemical variables, including ALP, ALT, lipase, electrolytes, proteins, albumin, and glucose (Xenoulis and Steiner, 2010). Interestingly, hypertriglyceridemia was recently associated with increased insulin resistance in a study of breed-associated hypertriglyceridemia in healthy Miniature Schnauzers (Xenoulis et al., 2011).

On admission, hypokalemia, normokalemia and hyperkalemia were observed in 8/22 (36%), 12/22 (54%), and 2/22 (9%) dogs, respectively. Even though it is common (55-76%) for dogs with DK-DKA to present with normal or even increased serum potassium (Macintire, 1981; Hume et al, 2006), total body potassium depletion must be considered in all DK/DKA cases (O'Brien, 2009). Hyperglycemia, metabolic acidosis, and hypoinsulinemia result in a shift of potassium from the intracellular to the extracellular space, while osmotic diuresis, vomiting and anorexia further exacerbate potassium losses (Boysen, 2008).

The $[Na_m]$ and $[Na_c]$ were below reference range in 81% and 62% of the dogs, respectively. Hyponatremia is a common finding in canine DK-DKA and it is mainly the result of the combined effect of dilution and osmotic diuresis (Kerl, 2001a). Severe hyperglycemia results in a water shift from the intracellular to the extracellular space that lowers sodium concentration, by dilution, in a predictable manner (Schermerhorn and Barr, 2006). On the other hand, hyponatremia results also from the excessive urinary sodium loss due to osmotic diuresis induced by glycosuria and ketonuria, while vomiting, diarrhea and anorexia further exacerbate sodium deficits. Attention must be paid in the presence of normal $[Na_m]$ and increased $[Na_c]$ in the face of severe hyperglycemia (>600 mg/dl) since it reflects a hyperosmolar state (Feldman and Nelson, 2004; O'Brien, 2009).

Serum BOH concentration was measured on

presentation and was used for treatment monitoring in 11 and 8 dogs, respectively. BOH is the predominant ketone body produced during DK-DKA and it is not detected by urine reagent strips, which instead provide a semiquantitative estimate of AcAc and less accurately of acetone that are excreted in the urine. Although ketonemia and ketonuria are usually detected concurrently (e.g., all 8 dogs with elevated BOH concentration were also ketonuric in the present study), ketonemia can occasionally be underestimated or even go undetected when urine reagent strips are solely used, since BOH:AcAc ratio can rise up to 20:1 in cases with severe hypovolemia and acidosis (Duarte et al., 2002). The use of ≤ 3.5 mmol/l as a cut off value for BOH in DKA is highly specific, when metabolic acidosis also exists, although it may be of slightly reduced sensitivity (Di Tommaso et al., 2009; Bresciani et al., 2014). Importantly, ketonuria may persist after resolution of ketonemia because BOH metabolizes to AcAc, making BOH measurement more suitable for treatment monitoring (Kerl, 2001b; Stojanovic and Ihle, 2011). Hand held meters for BOH concentration are available and they are considered accurate (Accu-Check Comfort, Roche; Precision Xtra, Abbot) for dogs (Hoening et al., 2009; Di Tommaso et al., 2009).

Aerobic bacterial urine cultures were positive in four dogs but two of them had inactive urine sediment and three did not presented clinical signs suggestive of UTI. The prevalence of the latter in DK-DKA and in uncomplicated canine DM is reported to range from 20 to 37% (Forrester et al., 1999; Hume et al., 2006) and occult infections (absence of pyuria, bacteriuria and compatible clinical signs) is common due to decreased neutrophilic chemotaxis (McGuire et al., 2002). Aerobic bacterial urine cultures are warranted in all dogs with DK-DKA, regardless of their clinical signs and the results of urine sediment examination (Feldman and Nelson, 2004).

In 74% of the dogs a disease, other than DK-DKA, was diagnosed and in 26% of them two or more diseases were documented. Concurrent diseases occur in up to 70% of dogs with DK-DKA and their presence is considered an important risk factor for

the development of this syndrome in both human and veterinary medicine (Kitabschi and Nyenwe, 2006, O'Brien, 2010). In a mortality prediction model of DK-DKA in humans, severe coexisting disease was a significant and independent predictor of mortality (Efstathiou et al., 2002). Thus, a comprehensive diagnostic investigation is of paramount importance in DK-DKA, since treatment of concurrent disorders accelerates the resolution of this syndrome (Feldman and Nelson, 2004). Various comorbidities may be encountered in dogs with DK-DKA, but acute pancreatitis, infections and hyperadrenocorticism are the most common (Hume et al., 2006).

Acute pancreatitis was diagnosed in 30% of the dogs and in previous studies prevalence up to 41% in DKA cases has been reported (Mackintire, 1993; Hess et al., 2000; Hume et al., 2006). DM is an important risk factor for the development of acute pancreatitis (Hess et al., 1999) and although the pathogenesis is not completely understood, a recent study provided evidence supporting a possible association between hypertriglyceridemia, a common occurrence in DM, and pancreatic inflammation (Xenoulis et al., 2011). Therefore, pancreatitis should always be assumed to co-exist in dogs with DK-DKA until proven otherwise (Feldman and Nelson, 2004).

Infections were identified in 13/23 (56.5%) dogs: four had UTI, four had superficial pyoderma, while leptospirosis, septic laryngeal granuloma, aspiration pneumonia, pyometra and prostatic abscess were diagnosed in one dog, each. A wide spectrum of infections, such as UTI, pneumonia, stomatitis, and abscesses, are considered leading precipitating factors for the development of DK-DKA (Chastain and Nichols, 1981; Hume et al., 2006) and in this series all the above infections, with the exception of superficial pyoderma that is typically not associated with systemic consequences, may have contributed to the development of this syndrome. Dysfunction of the innate and adaptive immunity along with hyperglycemia are thought to result in the increased susceptibility to infections in both human and veterinary DM and DK-DKA patients (Hess et al., 2000; Peleg et al., 2007).

In 3/23 dogs a diagnosis of HAC had been established prior to the development of DK-DKA, while

HAC was strongly suspected in three additional dogs based on clinical and clinicopathological abnormalities and adrenal ultrasonography, but since no adrenal function tests were conducted a diagnosis could not be reached. HAC is considered common in dogs with DM and DK-DKA accounting for approximately 10-15% of cases (Hess et al., 2000; Hume et al., 2006) and it has been associated with prolonged hospitalization and increased risk for euthanasia (Hume et al., 2006). Of note, the real prevalence of HAC in dogs with DK-DKA is hard to estimate because adrenal function tests, like low dose dexamethasone suppression test, are inaccurate (high rate of false-positive results) and therefore useless during DK-DKA (Hess et al., 2000); this was the reason that such testing was not performed in the three dogs suspect of HAC. Also, adrenal ultrasonography results should be cautiously interpreted, since bilateral adrenal enlargement can occur with chronic non-adrenal illness (Behrend and Melian, 2013). Currently, the recommended timing for evaluating patients with DK-DKA for HAC is after the resolution of ketoacidosis and the establishment of good glycemic control (Kerl, 2001a).

Regular insulin was the most common insulin used, followed by lispro. Standard protocols for treatment of DK-DKA recommend regular insulin, administered either IM or IV (Chastain and Nichols, 1981; Macintire, 1993). However, recently, an IV lispro-based protocol has been evaluated and found to be as safe and as effective as IV regular insulin treatment of DKA (Sears et al., 2012). Results of this study, even though based on a limited number of dogs, indicate that although no differences occurred in hospitalization time between dogs receiving lispro and dogs treated with regular insulin, the median time to resolution of ketoacidosis was significantly shorter in the former (Sears et al., 2012). In this case series the small number of dogs that received lispro and the inclusion of both healthy ketotic dogs and animals with severe ketoacidosis precluded any comparison between the two types of insulin, although overall effectiveness appeared to be similar. In one dog, lente, an insulin preparation with intermediate duration of action, was administered; ketonuria resolved after 4 days and the dog was discharged. Even though the use of interme-

diate-acting insulin is contraindicated in DKA, it can be a valid choice for otherwise healthy dogs with DK or when owners decline the in-hospital treatment of DK (Feldman and Nelson, 2004).

Fluids were administered in 78% of the dogs enrolled in this study and they are essential in the management of DK-DKA. Historically, the fluid of choice has been NS with or without the addition of dextrose, depending on serial blood glucose measurements. In five dogs the attending clinicians elected not to administer IV fluids and all these animals survived to discharge. These dogs were alert, without clinical signs of dehydration and they were eating and drinking voluntarily and thus they were considered as otherwise healthy ketotic dogs. Aggressive fluid administration may be unnecessary in these cases because insulin administration alone is often sufficient to achieve therapeutic success (Feldman and Nelson, 2004; Boysen, 2008).

Potassium was added to the IV fluids in 15/23 (65%) dogs, including the eight patients that were hypokalemic on admission. Median serum potassium concentrations tended to decrease during hospitalization even in dogs with normal or increased values on admission and four additional dogs became hypokalemic despite potassium supplementation in three of them. A rapid decrease in potassium concentration occurs in DK-DKA patients, especially in the first hours after the administration of IV fluids and of insulin, due to correction of hemoconcentration and metabolic acidosis, the insulin-mediated increase of cellular potassium uptake, and the ongoing losses (Hess, 2013). Therefore, potassium supplementation is recommended regardless of initial serum concentrations in both human and veterinary medicine, when normal kidney function exists. Close monitoring of serum potassium concentration is essential to adjust its concentration in IV fluids, and in the presence of severe hypokalemia insulin should be withheld until hydration status is improved and potassium levels are at least 3.5 mmol/L (Hume et al., 2006; Boysen, 2008; Nyenwe and Kitabchi, 2011; Koenig 2013).

Survival rate, duration of hospitalization and time to resolution of ketonuria in this series were similar with that reported in previous studies, but direct

comparison to these studies cannot be done since they included animals with confirmed metabolic acidosis only (Macintire, 1993; Hume et al., 2006). All three dogs that died were hypokalemic on admission or became hypokalemic during treatment, had metabolic acidosis and were diagnosed with combined comorbidities, invariably including pancreatitis. Pancreatitis, hypokalemia and the need for IV potassium supplementation were found to increase the duration of hospitalization in a recent study but they were not associated with survival (Hume et al., 2006). On the contrary, the severity of metabolic acidosis was directly associated with the outcome (Hume et al., 2006). In this study all animals with a confirmed normal metabolic status on admission survived to be discharged.

Asymptomatic hypoglycemia was the most common complication of treatment in the present study and was diagnosed 17% of the dogs. Hypoglycemia is considered common during DK-DKA treatment and is usually the result of overzealous insulin treatment (Kerl, 2001b). Another dog developed severe neurological complications on the second day and the owner declined further hospitalization. Neurological impairment is considered to be a rare complication during DK-DKA treatment in dogs, with cerebral edema being a potential cause (Schemerhorn and Barr, 2008). Even though the pathogenesis is not fully understood, rapid decrease of serum sodium concentration and OsmE are implicated, especially in dogs with renal impairment (Schemerhorn and Barr, 2008). Although hyperosmolality on admission was not documented in this case and no serial sodium and OsmE measurements were made, the presence of severe hyperglycemia (>600mg/dl) on admission makes abrupt changes in plasma tonicity the most probable reason for the development of cerebral edema. As a rule, OsmE should not be decreased faster than 3-4 mOsm/L/h in animals presented in a hyperosmolar state (Boysen, 2008).

Major limitation of this study, besides the small number of animals included, is that blood gas analysis was performed in a minority of dogs, and DKA was confirmed in only four cases. As a result this case series included animals with different clinical presentation, prognosis and treatment, which may affected certain aspects of the results, including the frequency of concurrent diseases, the duration of hospitalization and survival rates. Also, due to the retrospective nature and the large time period of the study diagnostic investigation was not uniform in all dogs and treatment varied significantly making some therapeutic choices not optimal according to today standards.

CONCLUSIONS

DK-DKA is a serious metabolic emergency that in most cases was seen in newly diagnosed diabetic dogs. Signs of uncomplicated DM (PU/PD, polyphagia, weight loss) were present for variable periods of time before additional severe systemic signs of DK-DKA appeared. Anemia, leukocytosis, increased ALP and ALT activities, hyperlipidemia and electrolyte imbalances were common clinicopathological abnormalities. A concurrent disease was diagnosed in the majority of cases and pancreatitis was the leading comorbidity. Even though, metabolic status affects prognosis and therapeutic options and it was available in a minority of dogs, it seems that fluid therapy, corrections of electrolyte imbalances and rapid-acting insulin therapy, along with management of the concurrent diseases, are essential to achieve a favorable outcome in animals with DK-DKA.

Conflict of Interest

None of the authors of this article has a financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of this paper.

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