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Canine diabetes mellitus risk factors: A matched case-control study

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ABSTRACT

Different subtypes of canine diabetes mellitus (CDM) have been described based on their aetiopathogenesis. Therefore, manifold risk factors may be involved in CDM development. This study aims to investigate canine diabetes mellitus risk factors. Owners of 110 diabetic dogs and 136 healthy controls matched by breed, sex, and age were interviewed concerning aspects related to diet, weight, physical activity, oral health, reproductive history, pancreatitis, and exposure to exogenous glucocorticoids. Two multivariate multivariable statistical models were created: The UMod included males and females without variables related to oestrous cycle, while the FMod included only females with all analysed variables. In the UMod, "Not exclusively commercial diet" (OR 4.86, 95%CI 2.2–10.7, $P < 0.001$) and "Overweight" (OR 3.51, 95%CI 1.6–7.5, $P = 0.001$) were statistically significant, while in the FMod, "Not exclusively commercial diet" (OR 4.14, 95%CI 1.3–12.7, $P = 0.01$), "Table scraps abuse" (OR 3.62, 95%CI 1.1–12.2, $P = 0.03$), "Overweight" (OR 3.91, 95%CI 1.2–12.6, $P = 0.02$), and "Dioestrus" (OR 5.53, 95%CI 1.9–16.3, $P = 0.002$) were statistically significant. The findings in this study support feeding not exclusively balanced commercial dog food, overweight, treats abuse, and diestrus, as main CDM risk factors. Moreover, those results give subside for preventive care studies against CDM development.

1. Introduction

Different subtypes of canine diabetes mellitus (CDM) have been described based on their aetiopathogenesis (Nelson and Reusch, 2014; Gilor et al., 2016). Unlike some years ago, there is only weak evidence supporting that most CDM cases developed immune-mediated diabetes (Ahlgren et al., 2014; Gilor et al., 2016). Nevertheless, DLA (dog leukocyte antigen) haplotypes were described with higher prevalence in predisposed breeds in comparison to less predisposed ones, and cell-mediated autoimmune destruction of beta-cells has been previously described in up to 50% of diabetic dogs (Catchpole et al., 2008). However, other causative factors have been related to CDM, such as: diseases of the exocrine pancreas, progesterone controlled GH overproduction, and secondary to hypercortisolism (Hoenig, 2002; Rand et al., 2004; Catchpole et al., 2005; Gilor et al., 2016). Despite obese dogs showing evidence of insulin resistance, beta-cell dysfunction secondary to insulin resistance seems unlikely. Moreover, no study has demonstrated how obesity can cause diabetes in dogs. Other characteristic that does not give support to a type 2 diabetes mellitus (T2DM) is pancreatic amyloidosis absence in obese diabetic dogs; however, glucotoxicity is an often-well-documented feature in CDM diagnosis (Nelson and Reusch, 2014).

Although genetic predisposition is likely important in CDM (Gilor et al., 2016), some environmental factors seem to be risk factors for diabetes development such as obesity, lack of exercise, and overfeeding (Klinkenberg et al., 2006). In this scenario, progesterone-related CDM cases are overexpressed in some regions worldwide where early elective spaying is not widespread practice. Other risk factors have been reported for both cats and humans (Rand et al., 2004; Temneanu et al., 2016; Goedecke et al., 2017). Given that CDM comprises heterogeneous disorders (Gilor et al., 2016) and is a multifactorial disease (Nelson and Reusch, 2014), this study aims to assess potential risk factors for diabetes by means of multivariable conditional logistic regression in a retrospective questionnaire based case-control study, and then, propose

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rational preventive strategies.

2. Material and methods

2.1. Case selection process

Medical data from all CDM cases diagnosed between 2004 and 2011 were prospectively selected from a Veterinary Teaching Hospital's Small Animal Endocrinology Service in southern Brazil. The diagnosis was based upon a fasting glycaemia > 11 mmol/L associated with glycosuria. Moreover, CDM clinical signs such us polyuria and polydipsia had to be documented. Patients with concomitant hyperadrenocorticism or hypothyroidism were not included.

2.2. Control selection process

For each diabetic dog in the study, at least one control (n:m) matched by sex, breed, and age at CDM diagnosis was randomly selected from computer files of the same general practice Veterinary Teaching Hospital. The underlying disease or reasons for the veterinary visit were not considered – only the fact that they had never been or were not diabetic.

2.3. Questionnaire

A questionnaire was previously developed, validated, and checked for accuracy in detecting owner's perception about CDM lifespan and risk factors exposure (Pöppl et al., 2013a). While case's variable exposure was registered prospectively during the study in standardized medical records, and questionnaire answers used for validation purposes, control owners were contacted to answer the questionnaire. To avoid recall bias, they were told that the questions considered the actual state of the dog. During prospective evaluation of cases, however, owners were asked questions regarding the dog's lifespan before CDM initial clinical signs. The control's questionnaires were applied over the telephone by trained interviewers and the interviews lasted 5 to 10 min, per the interviewees' eloquence. Despite the multiple-choice design of the questionnaire, all the answers were converted to dummy (dichotomous) variables showing exposure or non-exposure to the analysed factor.

2.4. Variables under study

The “Not exclusively commercial diet” variable was classified as feeding only homemade or homemade plus commercial food. The “Frequent meals” variable was considered as feeding three or more meals a day, while the “Treats abuse” and “Table scraps abuse” variables were classified as offering pet treats or table scraps daily or many times a day. The “Inactivity” variable was classified as owner-perceived low activity. Dogs that walked more than once weekly were considered exposed to the “Outside walks” variable; whereas dogs submitted to intense physical activity at least once a week were considered exposed to the “Intense physical activity” variable. A 4 or 5 owner-perceived body condition score (BCS) on a scale from 1 to 5 was regarded as exposure to “Overweight”. The “Halitosis” and “Dental calculus” variables were classified as intense perception by the owner, while the “Tooth brushing” and “Dental prophylaxis” variables were classified, respectively, as tooth brushing at least once a month, and at least one prophylaxis under general anaesthesia in the dog's lifetime.

The “Castration” variable was classified as gonadectomized animals, while the “Exposure to progestogens”, “Irregular oestrus cycle” and “Dioestrus” variables were investigated only in females. Those variables were classified as: exposure to progestogens in the past 6 months, inability of the owner to predict the patient's interoestrous interval due to unsynchronised oestrus, and heat occurrence within a period of three months, respectively. The “Pancreatitis” variable was classified as medical history of pancreatitis, while the “Glucocorticoids” variable was classified as frequent owner-related use of glucocorticoids by any route.

2.5. Statistical analysis

Since matching of cases and controls was used to control for known potential confounding variables such as sex, breed, and age, a conditional logistic regression was applied to explore the association between CDM and possible risk factors. Appropriateness of statistic methods for matched case-control studies that require specific analysis for dependent data (i.e., matched), as is the case of conditional logistic regression, was previously described (Niven et al., 2012). Odds ratio estimates and 95% confident intervals (95% CI) were reported, and *P*-values less than, or equal to 0.05 were considered statistically significant.

Conditional logistic regressions for a matched case-control design were performed using the PHREG procedure in SAS. Two sets of models were developed: 1) The Unisex model (UMod), which evaluated males and females without inclusion of variables related to the oestrous cycle; 2) The Female model (FMod), which evaluated only females, including all the investigated variables. For each statistical model, a univariable analysis was initially used to explore potential risk factors for CDM. Only the variables with a *P*-value < 0.20 were selected for inclusion in the multivariable analysis, being subsequently screened for potential collinearity by a correlation matrix. If factors were correlated (coefficients > 0.8), the variable believed to be most related to the outcome was selected.

Conditional logistic multivariable models were built assessing all the combinations of predictors identified in the univariable analysis by adding variables recursively and selecting the best model according to Akaike Information Criterion (AIC). After that, the final model was adjusted using backward elimination to remove non-significant ($P > 0.05$) variables from the combination that presented the best fit according to the AIC value (i.e., the one with the lowest value). Odds ratio (OR) with a 95% confidence interval (95% CI) was estimated by the models to assess the impact of factors on the outcome. This study was approved by the Ethics Committee on Animal Use in Research of UFRGS – protocol 18336.

3. Results

3.1. Population

Of the 120 diabetic dogs diagnosed between 2004 and 2011 at Hospital's Small Animal Endocrinology Service, 110 were initially included due to owners' agreement with the use of their pet's medical records. Seven owners could not be contacted at the time of CDM diagnosis and three owners refused to participate for distinct reasons. The mean age of the cases at the onset of diabetes was 10 ± 2.6 years (3 to 15 years). From a total of 143 randomly matched controls selected for the study, only seven owners refused to participate; therefore, 136 controls were eventually included after their owners' agreement to answer the questionnaire. A total of 23 breeds were identified among diabetic cases in this study as follow: Mongrel (37); Poodle (27); Cocker Spaniel (6); Labrador Retriever (5); Pinscher and Schnauzer (4 each); Beagle, Dachshund, Fox Terrier and Maltese (3 each); Basset Hound and Siberian Husky (2 each); Akita, Bichón Frisé, Boxer, Brittany, Chow-Chow, Dalmatian, Lhasa Apso, Rottweiler, Shi Tzu, Weimaraner and Yorkshire Terrier (1 each).

3.2. Unisex model

The UMod, including all males and females without variables related to the oestrous cycle, showed statistically significant associations ($P < 0.05$) between CDM and risk factors in the univariable analysis (Table 1) for the following variables: “Not exclusively commercial