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Assessment of the association between diabetes mellitus and chronic kidney disease in adult cats

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Abstract

Background: Diabetes mellitus is the main cause of chronic kidney disease (CKD) in humans. The relationship between the 2 diseases in cats is unclear.

Objective: To assess the association between diabetes and CKD in a population of adult cats.

Animals: Five hundred sixty-one cats that attended 2 veterinary centers in Gran Canaria, Spain, between 2014 and 2016.

Methods: Medical records were retrospectively reviewed. Cats aged 3 years or older, with sufficient data to define whether or not they had diabetes and CKD, were selected. Cats in critical condition, with dehydration or potential causes of prerenal azotemia and those treated with nephrotoxic drugs were excluded. Diagnosis of CKD was established when creatinine concentrations were >2 mg/dL, or serum creatinine 1.6-2 mg/dL and urine specific gravity <1.035, or serum creatinine 1.6-2 mg/dL and urine protein/creatinine ratio >0.4. Factors associated with CKD were identified through multivariate logistic regression analyses.

Results: Sixty-seven (11.9%) cats had CKD and 16 (2.9%) cats had diabetes. Sixty cats without diabetes (11%) and 7 with diabetes (44%) had CKD. Among the latter, both conditions were diagnosed simultaneously in 6 cases, whereas diabetes preceded CKD in the other. Multivariate analysis showed that diabetes was significantly associated with CKD (odds ratio = 4.47; 95% confidence interval, 1.51-13.28; *P* = .007). Other variables associated with CKD were age and mixed breed.

Conclusions and Clinical Importance: After adjusting for age, this study showed an association between diabetes and CKD in adult cats.

KEYWORDS
creatinine, feline, glucose, nephropathy

1 | INTRODUCTION

Diabetes mellitus is a common disorder in cats, with a prevalence ranging from 0.43% to 1.24%.[1-3] Around 80% of cats with diabetes have type 2 diabetes, characterized by insulin resistance and dysfunction of pancreatic

beta cells.[4] As in humans, risk factors for type 2 diabetes in cats include obesity, age, and genetic factors.[5-7] In humans, diabetes is the leading cause of chronic kidney disease (CKD).[8] Although the pathophysiological mechanisms of diabetes-related CKD are not fully known, it is accepted that hyperglycemia, advanced glycation products, oxidative stress, inflammatory cytokines, and profibrotic growth factors are involved in renal injury.[8]

Disorders associated with CKD in cats include diseases of the lower urinary tract, renal lymphoma, infections, hyperthyroidism, nephrotoxic drugs, and genetic kidney diseases, although often the cause of CKD is unknown.[9] Although both CKD and type 2 diabetes are common disorders in cats, the relationship between the 2 has not been investigated in depth; indeed, some studies have suggested that diabetes plays little or no role in the development of CKD.[10,11]

The aim of this study was to assess the association between CKD and diabetes in a population of cats attending 2 veterinary centers in the island of Gran Canaria (Spain).

2 | MATERIALS AND METHODS

Clinical records of cats attending at University Veterinary Teaching Hospital and an Endocrinology Clinic in Gran Canaria between 2014 and 2016 were reviewed.

All cats selected were 3 years or older and presented sufficient data to define whether or not they had diabetes and CKD. Given the rarity of diabetes in younger cats, only adult animals were included.[12] Animals without available biochemical data, but with no clinical history of CKD or diabetes, were considered to be free of these diseases. In cases where CKD, diabetes, or both were suspected, but in which the clinical history and laboratory tests were insufficient to establish either diagnosis, the owners were contacted by telephone. When this was not possible, the animals were excluded from the study.

Diabetes was defined by typical clinical signs (polyuria/polydipsia, polyphagia, weight loss), persistent hyperglycemia, or fructosamine >400 mmol/L. Persistent hyperglycemia was defined as blood glucose concentrations above 250 mg/dL for at least 2 weeks.[12,13] Considering the guidelines proposed by the International Society of Feline Medicine (ISFM)[14] and the International Renal Interest Society,[15] CKD was considered in cats with serum creatinine ≥1.6 mg/dL, plus urine specific gravity (USG) <1.035 or urine protein/creatinine (UPC) ratio >0.4. Where USG and UPC ratio were not recorded, criteria to define azotemia used by other investigators were followed,[16,17] and definitive diagnosis of CKD was established only in cases with creatinine values >2 mg/dL. Cats in critical condition, with dehydration or potential causes of prerenal azotemia (trauma, intoxication, fever, infection, urinary obstruction), and those treated with nephrotoxic drugs were excluded.

In addition to age, other data such as sex, breed, and weight were recorded. In cats with CKD and diabetes, the existence of other concurrent diseases was also registered.

2.1 | Statistical analysis

Categorical variables were expressed as frequencies and percentages, and continuous variables as median and interquartile range (IQR = 25th-75th percentile). Percentages were compared using the chi-square (χ^2) test or the Fisher exact test, as appropriate, and medians were compared with Wilcoxon's test for independent data. To identify factors independently associated with CKD, multivariate logistic regression analyses were performed, entering all the variables that showed significant associations with the outcome in univariate analyses. Then, a best subset regression procedure was used to identify the most suitable and parsimonious multivariate logistic model, that is, the 1 with the lowest Bayesian information criterion (BIC), which is a parameter of the goodness of fit of the models, defined as:

$$BIC = -2 \times loglik + (\log N) \times d,$$

with loglik being the log-likelihood, N the sample size, and d the number of variables in the model. The final model was summarized as coefficients (SE), P-values (likelihood ratio test), and odds ratios (ORs), which were estimated by confidence intervals (CIs) at 95%. Statistical significance was set at $P < .05$. Data were analyzed using the R package, version 3.3.1 (R Development Core Team, 2016).

3 | RESULTS

A total of 1834 cases were reviewed (1582 from the University Veterinary Teaching Hospital and 252 from the Endocrinology Clinic). Of these, 592 (567 from the University Veterinary Teaching Hospital and 25 from the Endocrinology Clinic) were excluded because of insufficient data about age, CKD, or diabetes, or because they were receiving nephrotoxic drugs. Another 681 cats were excluded (1 with CKD and none with diabetes) because they were under 3 years old.

Of the final population of 561 cats, 67 (11.9%, 35 males, median age 11.4 [8.0-14.5] years) had CKD, and 16 (2.9%, 14 males, median age 11.5 [9.1-14.9] years) had diabetes. The proportion of cats with CKD and diabetes was 12.2% and 2.5% in the University Veterinary Teaching Hospital and 11.1% and 4.3% in the Endocrinology Clinic, respectively. Among cats with CKD, abnormal results of USG or UPC were registered in 21 cases, while diagnosis was exclusively based on serum creatinine in 45. Of these, 29 presented with moderate or severe azotemia, whereas 16 had only slightly increased serum creatinine concentrations (<2.8 mg/dL). No laboratory tests were available in 1 additional case, but the clinical record reported that the cat had been euthanized because of CKD. This information was confirmed by the owner, who also stated that no other diseases, including diabetes, had been reported by the veterinarian. Among the cats with diabetes, persistent hyperglycemia and increased fructosamine, or increased fructosamine were recorded in all cases.

Seven of the diabetic cats (44%), 4 from the University Veterinary Teaching Hospital and 3 from the Endocrinology Clinic, also met the criteria for the diagnosis of CKD and 6 of them (86%) were males. In

TABLE 1 Main laboratory results in cats with chronic kidney disease, diabetes, or both

	DM and no CKD N = 9	No DM and CKD N = 60	DM and CKD N = 7	P*
Glucose, mg/dL	510 (423-610)[a]	128 (100-156)[b]	503 (422-600)[a]	<.001
Creatinine, mg/dL	1.2 (0.9-1.4)[a]	4.1 (2.7-6.2)[b]	2.2 (2.0-2.3)[c]	<.001
Urea, mg/dL	64 (51-84)[a]	175 (104-274)[b]	116 (64-124)[a]	<.001

Data are medians (interquartile range). Different superscripts indicate significant differences (P < .05).
Abbreviations: CKD, chronic kidney disease; DM, diabetes mellitus.
*Kruskal-Wallis test.

TABLE 2 Characteristics of the cats according to the presence or absence of chronic kidney disease

	Total N = 561	Chronic kidney disease		P
		No N = 494	Yes N = 67	
Age, y	7.7 (4.7-11.6)	7.0 (4.5-11.0)	11.4 (8.0-14.5)	<.001
Mature (≥7 years)	314 (56.0)	257 (52.0)	57 (85.1)	<.001
Sex, male	279 (49.8)	244 (49.4)	35 (53.0)	.6
Breed				<.001
Domestic Shorthair	426 (80.7)	375 (81.3)	51 (76.1)	
Persian	40 (7.6)	40 (8.7)	0	
Mixed	24 (4.5)	15 (3.3)	9 (13.4)	
Siamese	16 (3.0)	12 (2.6)	4 (6.0)	
Others	22 (4.2)	19 (4.1)	3 (4.5)	
Diabetes mellitus	16 (2.9)	9 (1.8)	7 (10.4)	.001
Veterinary centers				.8
University Veterinary Teaching Hospital	444 (79.1)	390 (78.9)	54 (80.6)	
Endocrinology Clinic	117 (20.9)	104 (21.1)	13 (19.4)	

Qualitative variables are expressed in percentages.

5 of these 7 cats, plasma creatinine concentration was >2 mg/dL, and in the other 2, it was 1.8 mg/dL (1 with increased UPC ratio, and the other with low USG). In 6 of the 7 cats with CKD and diabetes, both diseases were diagnosed simultaneously, while in the other cat, CKD was detected 10 years after diabetes. In 5 of these cases, an additional risk factor that might have contributed to the worsening of renal function was identified (chronic periodontal disease in 2 cats, and pancreatitis, megacolon and primary hyperaldosteronism in 1 cat each).

Plasma creatinine and urea concentrations were higher in cats with CKD without diabetes than in cats with both diseases (Table 1). Table 2 shows the clinical and demographic characteristics of the study population, according to the presence or absence of CKD. Older age, lower weight, mixed breed, and diabetes were significantly associated with CKD. Due to the retrospective nature of the study, it was not possible to determine the breed of the progenitors of the mixed breed cats. In a multivariate logistic regression analysis including the variables that had shown a significant association with CKD in the univariate analysis, diabetes maintained a significant association with CKD (Table 3). To assess the robustness of these results, 2 sensitivity analyses were performed. First, given the limitations regarding the

TABLE 3 Results of multivariate logistic regression analysis adjusted for age for the factors associated with the diagnosis of feline chronic kidney disease shown in Table 1 for a population of 561 adult cats

	Coefficient (SE)	P	OR (95% CI)
(Intercept)	−3.672 (0.364)	<.001	–
Age, per year	0.157 (0.031)	<.001	1.171 (1.103-1.243)
Diabetes mellitus	1.627 (0.559)	.004	5.088 (1.702-15.205)
Mixed breed	1.753 (0.472)	<.001	5.773 (2.291-14.548)

Abbreviations: CI, confidence interval; OR, odds ratio; SE, standard error.

assessment of the origin of the mixed breed cats, a multivariate model including only age and diabetes was created. In this model, the association between diabetes and CKD remained significant (OR for diabetes, 4.47; 95% CI, 1.51-13.28; P = .007). Additionally, because the ISFM guidelines recommend the assessment of USG to establish the diagnosis of CKD, the analysis was repeated excluding 16 cats (2 with diabetes) with only slightly increased creatinine concentrations (<2.8 mg/dL), in which no USG or UPC ratio data were available, and excluding the 1 case without a laboratory test recorded. Also in this case, the association

between diabetes and CKD remained significant (OR, 4.63; 95% CI, 1.39-15.37; P = .01).

4 | DISCUSSION

In this study assessing 561 adult cats attending 2 veterinary centers, the frequency of CKD was higher among those with diabetes (44%) than among those without diabetes (11%). Multivariate analyses, adjusting for age and breed, showed a significant association between diabetes and CKD. Although these results were obtained from a small population of diabetic cats, they suggest that CKD could be a complication of diabetes in cats as in humans, in whom the prevalence of CKD is 20%-30% in diabetic populations.[19,20] Few studies have assessed the association between CKD and diabetes in cats. One of the strengths of the present study is the use of multivariate logistic regression analyses adjusting for age, because both diseases could arise concurrently in adulthood.

Given the retrospective nature of the study and that no specific procedures were performed to identify the etiology of CKD in diabetic cats, no direct causal relationship between diabetes and CKD can be inferred. The fact that cats with CKD without diabetes had higher concentrations of creatinine and urea might suggest that CKD is milder in cats that also have diabetes or that it is detected earlier and could be due to closer veterinary follow-up.

Our findings are at odds with those of previous studies which have suggested that there is no association between diabetes and CKD in cats. However, few studies have evaluated the presence of diabetes in large populations of cats with CKD. In 2 retrospective epidemiological studies, no relationship was found between diabetes and CKD.[21,22] In the first of these studies, analyzing a large sample, a prior diagnosis of diabetes was associated with a lower risk of CKD in a multivariate logistic regression analysis.[21] The authors stressed that this was an unexpected finding and could not suggest any explanation. The second epidemiological study was a case-control study of 92 cats with CKD and 92 age-matched controls. Although prior diagnosis of diabetes was more frequent in the group with CKD, the differences were not statistically (OR, 2; 95% CI, 0.37-11) significant.[22] Other authors have assessed this issue using biomarkers or renal histopathology. There were no significant differences in cystatin C concentrations between cats with diabetes and healthy cats; however, 39% of the cats with diabetes (and none of the healthy cats) had proteinuria.[10] Similarly, in 66 cats with diabetes and 11 healthy controls, there was a higher prevalence of proteinuria and microalbuminuria in the diabetic cats (70% vs 35% and 70% vs 39%, respectively).[23] Additionally, a postmortem study comparing diabetic cats with controls matched for age, sex, body weight, and breed did not find significant differences between groups.[11] On the basis of the concentrations of creatinine and urea obtained antemortem, 23.3% of cats with diabetes and 31.6% of controls were considered to have CKD.[11] The differences observed between humans and cats might be a consequence of the shorter life expectancy in cats and a shorter time of exposure to diabetes.[11] Renal lesions in people with diabetes are mainly characterized by a

disorder of the glomeruli, with basal membrane thickening, increased mesangial matrix and mesangial nodules (Kimmelstiel-Wilson nodules).[24] Patterns of ultrastructural alterations occur in the kidneys of patients with earlier stages of CKD associated with diabetes which differ from those usually considered as characteristic of diabetic nephropathy. Indeed, glomerular lesions are present in only 30% of cases, while the rest of the patients present mainly tubulointerstitial lesions, if any.[24,25] Therefore, the histological lesions observed in cats might be more similar to those described in humans with a shorter exposure to diabetes.

In addition to diabetes, age and breed were also associated with CKD in our population. The prevalence of CKD increases with age, reaching 30%-40% in cats older than 10 years.[9] All the animals included in the present analysis were adult, and 85.1% of those with CKD were over the age of 7 years. The association between mixed breed and CKD is difficult to interpret, but it is possible that it might reflect a specific association conferred by 1 or more breeds overrepresented in mixed breed crosses but not identified in this study. There is an increased risk of CKD in Persian, Abyssinian, and Siamese cats.[9]

The present study has several limitations, deriving mainly from its retrospective nature. The cats seen at the 2 veterinary centers selected are not necessarily representative of the general population. Some cases had to be excluded due to missing data, and it is possible that others with subclinical forms of CKD, diabetes, or both were classified as healthy. Furthermore, the diagnosis of CKD could not be established precisely in some cases in which USG was not available. In this regard, however, the multivariate logistic regression analysis that excluded cases with milder azotemia in which urine was not available was consistent with the analysis performed in the total population. Finally, the diagnosis of mild CKD in cats with diabetes is complicated by the fact that glucosuria could reduce USG.[10] However, most of the cats with CKD and diabetes had serum creatinine concentrations >2 mg/dL, the cutoff value used in many studies to define azotemia in this species.[16,17,26]

CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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REFERENCES

1. O'Neill DG, Church DB, McGreevy PD, et al. Prevalence of disorders recorded in cats attending primary-care veterinary practices in England. *Vet J*. 2014;202(2):286-291.
2. Prahl A, Guptill L, Glickman NW, Tetrick M, Glickman LT. Time trends and risk factors for diabetes mellitus in cats presented to veterinary teaching hospitals. *J Feline Med Surg*. 2007;9(5):351-358.
3. McCann TM, Simpson KE, Shaw DJ, et al. Feline diabetes mellitus in the UK: the prevalence within an insured cat population and a questionnaire-based putative risk factor analysis. *J Feline Med Surg*. 2007;9(4):289-299.
4. Nelson RW, Reusch CE. Animal models of disease: classification and etiology of diabetes in dogs and cats. *J Endocrinol*. 2014;222(3):T1-T9.
5. Gilor C, Niessen SJ, Furrow E, DiBartola SP. What's in a name? Classification of diabetes mellitus in veterinary medicine and why it matters. *J Vet Intern Med*. 2016;30(4):927-940.
6. Forcada Y, Holder A, Church DB, Catchpole B. A polymorphism in the melanocortin 4 receptor gene (MC4R:c.92C>T) is associated with diabetes mellitus in overweight domestic shorthaired cats. *J Vet Intern Med*. 2014;28(2):458-464.
7. Lederer R, Rand JS, Jonsson NN, Hughes IP, Morton JM. Frequency of feline diabetes mellitus and breed predisposition in domestic cats in Australia. *Vet J*. 2009;179(2):254-258.
8. Pyram R, Kansara A, Banerji MA, Loney-Hutchinson L. Chronic kidney disease and diabetes. *Maturitas*. 2012;71(2):94-103.
9. Reynolds BS, Lefebvre HP. Feline CKD pathophysiology and risk factors—what do we know? *J Feline Med Surg*. 2013;15(1):3-14.
10. Paepe D, Ghys LF, Smets P, et al. Routine kidney variables, glomerular filtration rate and urinary cystatin C in cats with diabetes mellitus, cats with chronic kidney disease and healthy cats. *J Feline Med Surg*. 2015;17(10):880-888.
11. Zini E, Benali S, Coppola L, et al. Renal morphology in cats with diabetes mellitus. *Vet Pathol*. 2014;51(6):1143-1150.
12. Sparkes AH, Cannon M, Church D, et al. ISFM consensus guidelines on the practical management of diabetes mellitus in cats. *J Feline Med Surg*. 2015;17(3):235-250.
13. Bennett N, Greco DS, Peterson ME, Kirk C, Mathes M, Fettman MJ. Comparison of a low carbohydrate low fiber diet and a moderate carbohydrate high fiber diet in the management of feline diabetes mellitus. *J Feline Med Surg*. 2006;8(2):73-84.
14. Sparkes AH, Caney S, Chalhoub S, et al. ISFM consensus guidelines on the diagnosis and management of feline chronic kidney disease. *J Feline Med Surg*. 2016;18(3):219-239.
15. IRIS. *Staging of CKD [Internet]*. UK: International Renal Interest Society; 2016: http://www.iris-kidney.com/guidelines/index.html.
16. Chakrabarti S, Syme HM, Elliott J. Clinicopathological variables predicting progression of azotemia in cats with chronic kidney disease. *J Vet Intern Med*. 2012;26(2):275-281.
17. Williams TL, Dillon H, Elliott J, Syme HM, Archer J. Serum Cystatin C concentrations in cats with hyperthyroidism and chronic kidney disease. *J Vet Intern Med*. 2016;30(4):1083-1089.
18. Morgan JA, Tartar JF. Calculation of the residual sum of squares for all possible regressions. *Technometrics*. 1972;14:317-325.
19. American Diabetes Association. Nephropathy in diabetes. *Diabetes Care*. 2004;27(Suppl. 1):S79-S83.
20. Bailey RA, Wang Y, Zhu V, Rupnow MF. Chronic kidney disease in US adults with type 2 diabetes: an updated national estimate of prevalence based on kidney disease: improving global outcomes (KDIGO) staging. *BMC Res Notes*. 2014;7:415.
21. Greene JP, Lefebvre SL, Wang M, Yang M, Lund EM, Polzin DJ. Risk factors associated with the development of chronic kidney disease in cats evaluated at primary care veterinary hospitals. *J Am Vet Med Assoc*. 2014;244(3):320-327.
22. Barlett PC, Van Buren JW, Barlett AD, Zhou C. Case-control study of risk factors associated with feline and canine chronic kidney disease. *Vet Med Int*. 2010;2010:957570. https://doi.org/10.4061/2010/957570.
23. Al-Ghazlat SA, Langston E, Greco DS, et al. The prevalence of microalbuminuria and proteinuria in cats with diabetes mellitus. *Top Companion Anim Med*. 2011;26(3):154-157.
24. Fioretto P, Mauer M. Histopathology of diabetic nephropathy. *Semin Nephrol*. 2007;27(2):195-207.
25. Fioretto P, Mauer M, Brocco E, et al. Patterns of renal injury in type 2 NIDDM diabetic patients with microalbuminuria. *Diabetologia*. 1996;39:1569-1576.
26. Van den Broek DH, Chang YM, Elliott J, Jepson RE. Chronic kidney disease in cats and the risk of total hypercalcemia. *J Vet Intern Med*. 2017;31(2):465-475.