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A two-center, randomized controlled trial to determine the effect of 12 weeks of caloric restriction with a novel diet in overweight cats with diabetes mellitus

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Abstract

Background: **Obesity is associated with insulin resistance and affects glycemic control in diabetic patients.**

Hypothesis/Objectives: **Assess the impact of 12-week caloric restriction on remission and glycemic control in overweight diabetic cats using a prospective, randomized controlled trial.**

Animals: **Seventy-two overweight (body condition score ≥ 6/9) client-owned insulin-treated diabetic cats, randomized either to caloric restriction (intervention, 32; target approximately 2% weekly weight loss) or body weight maintenance (control, 40).**

Methods: **All cats received a novel therapeutic diabetic diet, suitable for weight reduction, for 12 weeks (%metabolizable energy [protein/fat/nitrogen-free extract]: dry [49.4/24/26.6]; wet [63.2/25.3/11.5]). Physical examination, serum biochemistry, home blood glucose curves (BGC), diabetic clinical score, and quality of life questionnaires were performed on weeks: −1, 4, 8, and 12. Insulin dose was recorded and glycemic variability (SD of BGC) was calculated. Induction of diabetic remission was the primary outcome measure. Data were analyzed using regression and linear mixed models.**

Results: **By week 12, intervention had 2.1 times higher probability of remission (16/32) compared with controls (12/40, $P = .04$). Weight loss was 7.2% (95% confidence interval [CI], 5.7-8.7) for the intervention versus 2.7% (95% CI, 1.3-4.1, $P < .001$) for controls. For cats not achieving remission, glycemic variability decreased 45% (95% CI, 26-65) and 7% (95% CI, 16-21) for intervention and control cats, respectively ($P = .01$), insulin-dose decreased by 36% (95% CI, 2-70) for intervention and increased 28% (95% CI, 3-53, $P = .004$) for controls.**

Conclusions and clinical importance: **Caloric restriction, using a therapeutic diabetic diet suitable for weight reduction increased the probability of remission and improved glycemic control in overweight diabetic cats.**

Keywords feline, obese, weight loss, remission

Abbreviations AWIS, average-weighted impact score; BCS, body condition score; BG, blood glucose; BGC, blood glucose curve; BW, body weight; DCS, diabetic clinical score; DIAQoL-pet, diabetes mellitus associated quality of life; DM, diabetes mellitus; EBVS, European Board Of Veterinary Specialisation; FDR, false discovery rate; FEDIAF, European pet food industry; fPLI, feline pancreatic lipase immunoreactivity; GV, glycemic variability; IGF-1, insulin-like growth factor; IR, insulin resistance; IRIS, International Renal Interest Society; ITT, intention-to-treat; MCS, muscle condition score; MER, maintenance energy requirement; NFE, nitrogen-free extract; PZI, protamine zinc insulin; QA, question A; QB, question B; RVC, Royal Veterinary College, London, United Kingdom; SDMA, symmetric dimethylarginine; T4, serum thyroxine; UCPH, University of Copenhagen, Copenhagen, Denmark

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Introduction

Diabetes mellitus (DM) is a common endocrinopathy in cats with increasing prevalence.[1–3] Like type 2 DM in humans, DM in cats develops from a combination of peripheral insulin resistance (IR) and inadequate insulin secretion secondary to pancreatic β-cell dysfunction.[4]

Obesity is a major risk factor for the development of type 2 DM in humans, inducing metabolic derangements and low-grade inflammation, which can lead to insulin resistance and pancreatic β-cell toxicity.[5,6] Similarly, the peripheral IR and adipokine derangements induced by obesity make it an important risk factor for DM in cats.[7–10] Unlike type 1 DM, the β-cell exhaustion and destruction in type 2 DM can be arrested and partially reversed with timely treatment, making diabetic remission possible for humans and cats.[10,11]

Diabetic remission improves the quality of life (QoL) for both cats with DM and their owners.[12–14] Although no single factor definitively promotes successful remission,[15] low-carbohydrate diets (<25% dry matter [DM], <15% metabolizable energy [ME], <5 g/100 kcal)[16] and weight loss[17] have supportive roles. Although several purpose-formulated low-carbohydrate diets are available for diabetic cats, few are suitable for caloric restriction. In humans with type 2 DM, caloric restriction using low calorie diets and controlled weight reduction can improve glycemic control and increase the likelihood of diabetic remission[18–21] by decreasing peripheral IR and glucotoxicity, allowing β-cells to recover and produce sufficient insulin. To our knowledge, a similar approach has not yet been investigated in diabetic cats, specifically the ability of a therapeutic weight loss diet, formulated for diabetic cats, to induce remission, when given in combination with a longer-acting insulin preparation.

Our hypothesis was that a 12-week intentional marked caloric restriction under veterinary supervision would increase the rate of diabetic remission in insulin-treated overweight diabetic cats. The primary outcome measure was clinical remission, whereas secondary outcome measures were related to glycemic control, safety, and the magnitude of overall weight loss.

Materials and methods

Study design

Our study was a prospective, 2-center, open-label randomized controlled trial to determine the effect of a 12-week caloric restriction on clinical remission in diabetic cats in overweight condition (body condition score [BCS] $\geq$ 6/9). The trial was not registered in a clinical trials register before commencement. Client-owned cats were recruited at two sites: University of Copenhagen, Copenhagen, Denmark (UCPH) and Royal Veterinary College, London, United Kingdom (RVC), between March 2021 to January 2023. After the 12-week intervention, cats were monitored for a further 9 months, with follow-up of all cases being completed by January 2024. The study protocol was approved by the local ethics committee at the Department of Veterinary Clinical Sciences, University of Copenhagen (Approval No. 2021-2); the Clinical Research Ethical Review Board at the Royal Veterinary College, United Kingdom (Approval No. URN 2020 2020-3); and Royal Canin's Ethical Review Committee, Aimargues, France (approval No. 250820-34). Written informed consent was obtained from all owners before enrollment, and owners could withdraw their cats from the study at any time. All collected blood samples were used for clinical purposes. The study was conducted and reported according to the standards of reporting randomized trials in pets (PetSORT) guidelines.[22,23] One study author (AJG), not directly involved in case recruitment and monitoring, ensured that the guidelines were followed and that reporting was accurate (Table S1).

Cat recruitment and follow-up visits

Client-owned cats, with BCS $\geq$ 6/9, diagnosed with DM within the past 24 months, were recruited via social media, local publicity, and through referring veterinary practices. Recruited cats were either diagnosed by trial veterinarians in accordance with the Agreeing Language in Veterinary Endocrinology (ALIVE) consensus definition,[24] or had been previously diagnosed and were receiving current insulin treatment. Full details of the eligibility and exclusion criteria are provided in Table 1.

Before inclusion (week −1), a history was taken and physical examination performed, including body weight (BW), a 9-point BCS[25] and a 4-point muscle condition score (MCS; A: normal muscle mass; or B: mild; C: moderate; or D: marked muscle wasting[26]). Both BCS and MCS were performed by the principal investigators, who received similar training at both sites for consistency. Overweight and obese condition were defined as BCS 6-7/9 and 8-9/9, respectively. Electronic cat scales (MTB20; precision, ±5 g; range, 0.025-20.000 kg; Adam Equipment, Milton Keynes, United Kingdom), were provided to all owners, after instructions on how to accurately weigh their cats. All cats were weighed weekly, and diet allocation was adjusted as described below. Blood and urine were collected for CBC, serum biochemistry, serum total thyroxine (T4) concentration, feline pancreatic lipase immunoreactivity (fPLI), insulin-like growth factor (IGF-1), and urinalysis (Figure S1). Owners completed the diabetic clinical score (DCS) questionnaire (Table S2),[24] and the Diabetic QoL (DIAQoL) pet survey tool (Table S3).[27] Details regarding screening and test procedures are provided in Figure S1.

Cats not previously treated with protamine zinc insulin (PZI, Boehringer Ingelheim, Duluth, GA) were transitioned to PZI, at an initial dosage of 0.2-0.4 U/kg twice daily at least 3 weeks before trial entry.

Revisits were scheduled for weeks 4, 8, and 12 (Figure S1), with assessments performed including history, physical examination, DCS (Table S2) and DIAQoL tool (Table S3), serum biochemistry, serum fructosamine concentration, and fPLI. At week 12, CBC and urinalysis also were performed. The initial plan was for all cases to be seen at UCPH or RVC at every re-examination. However, if owners had logistical difficulties, the week 4 or week 8 examinations could be undertaken by their own veterinarians, and the owner subsequently contacted by phone to retrieve the relevant data.

Randomization, allocation, and blinding

Cats meeting all eligibility criteria were enrolled and randomized to the intervention (caloric restriction) or control (caloric allocation for maintenance) groups. The duration of the intervention was 12 weeks, with a 1-week food adaptation during which cats were fed the test diet at their estimated maintenance energy requirement (MER). Cats were randomized using a single randomization program in REDCap,[28,29] stratified by both trial centers

Table 1 Final eligibility criteria for the randomized controlled trial.

Inclusion criteria: screening
Adult cat (>1 year)
BCS ≥ 6/9
Duration of continually having diabetes mellitus >4 weeks and <24 months
Treatment with protamine zinc insulin at least 3 weeks prior to starting the intervention
If previously in remission, the cat must since have relapsed and not regained remission despite one month of insulin treatment.
No glucocorticoid treatment within 4 weeks prior to diagnosis, or during the period between diabetes recruitment and inclusion in the study
Not be deemed to be repeatedly cycling between clinical remission and relapse.
Not deemed to be at increased risk of complications such as ketoacidosis or hypoglycemia
No evidence of uncontrolled hyperthyroidism (T4 < 55 nmol/L)
No evidence of uncontrolled pancreatitis or active gastrointestinal signs (based on abnormal serum spec fPL and concomitant clinical signs)
No evidence of active gastrointestinal disease based on clinical signs (eg, frequent vomiting, diarrhea and unexplained weight loss) 6 months prior to enrolment
CKD IRIS stage ≤2.
No evidence of hyperadrenocorticism based on clinical signs
No evidence of hypersomatotropism (IGF-1 < 1000 ng/ml)
No evidence of food intolerances or other dietary problems that might affect the tolerance to a dietary change
No evidence of liver disease, (liver enzyme activity < 3 times the upper limit of the reference interval) and albumin concentration < reference interval in stable diabetic cat
Exclusion criteria: post inclusion
Cat not eating the diet
Lacking owner compliance
Noncompliant cat (eg, Unable to handle)
Severe clinical signs of illness

Abbreviations: BCS = body condition score; CKD = chronic kidney disease; IGF-1 = insulin-like growth factor 1; spec fPL = feline-specific pancreatic lipase immunoreactivity; T4 = thyroxine.

(RVC vs. UCPH) and BCS at 2 levels (overweight: BCS 6-7/9; obese: 8-9/9). Within each level, new participants had an equal chance of being assigned to either intervention or control. Because of the nature of the study, neither owners nor study investigators could be blinded.

Test diet

All cats were fed a novel wet or dry therapeutic diet, formulated for diabetic cats, and suitable for weight reduction (Royal Canin SAS, Aimargues, France, Table 2).

Initial daily diet allocation was calculated for each cat using a tailored data collection tool in REDCap,[30] based on the theoretical energy density of the diets (3379 and 597 kcal/kg for the dry and wet diets, respectively). The intervention group received 50 kcal/kg ideal body weight$^{0.711}$.[31] The food allocation was adjusted aiming for an approximately 2% per week weight loss rate (Table S4). Cats in the control group initially received 75 kcal/kg$^{0.67}$ current BW (neutered or indoor cats) according to European pet food industry guidelines, with the aim of maintaining their BW.[32] This food allocation was adjusted if BW change exceeded 2% of initial BW (S4). In both groups, caloric allocation was adjusted for weight maintenance if the cats reached BCS 5/9.

The daily allocation was fed as wet food, dry food, or a mix of both, according to owner and cat preference. For accuracy, owners weighed food on electronic kitchen scales (Digital scale 500 g; precision, 0.1 g; Soehnle professional, Backnang, Germany), ideally dividing this allocation into multiple meals, with a larger meal given at time of insulin injection. In multi-cat households, chip-responsive automated feeders (SureFeed; Sure Petcare, Cambridge, United Kingdom) were used. For both groups, a maximum of 10% of the daily energy allocation could be fed as pre-approved treats (eg, zucchini, cucumber, or boiled chicken). The test diets were formulated to be low in starch, high in protein, with low energy density and increased vitamin and mineral content relative to energy, to ensure sufficient intakes of amino acids and micronutrients during therapeutic weight reduction. Following European regulation for dietetic pet foods, the essential nutritional characteristics of feeds for two particular nutritional purposes, regulation of glucose supply (DM) and reduction of excessive body weight, were met.[33] Owners recorded their cats' daily food intake in diaries, that were checked at each re-examination to ensure compliance.

Collection of clinical samples and laboratory analyses

Blood was collected aseptically by jugular venipuncture into EDTA and serum gel tubes. Plasma and serum were separated within 30 min of collection by centrifugation at 4000 × *g* for 3 (RVC) or 5 min (UCPH). Surplus material was stored for later analyses (−80°C). Urine was collected by ultrasound- or palpation-guided cystocentesis for routine urinalysis, and bacterial culture (if clinical signs consistent with urinary tract infection were present).

Routine blood and urine samples were analyzed at the veterinary diagnostic laboratories of the UCPH and RVC, respectively.

Table 2 Average composition of study diets fed to overweight diabetic cats.

	Dry diet			Wet diet		
	g/100 g as fed	g/1000 kcal	% ME	g/100 g as fed	g/1000 kcal	% ME
Protein	44.7	132.4	49.4	10.1	158.7	63.2
Carbohydrate (NFE)	24.2	71.5	26.6	1.6	29.0	11.5
Digestible carbohydrate fraction (starch)	14.1	41.7	-	<0.5	<0.8	-
Fat	8.9	26.5	24.0	1.7	26.2	25.3
Total dietary fiber	17.5	52.0	-	1.8	27.8	-
Crude fiber	7.9	23.4	-	0.7	10.5	-
Metabolizable energy (NRC 2006, TDF)	3379 kcal/kg			636 kcal/kg		
Formula composition	Dehydrated poultry protein, wheat gluten, vegetable fibers, maize starch, soya protein isolate, maize gluten, hydrolyzed poultry protein, minerals, psyllium husks and seeds, animal fats, chicory pulp, yeasts products, algal oil *Schizochytrium* sp. (source of DHA), fructo-oligo-saccharides, fish oil, marigold extract (source of lutein).			Poultry by-products, pork by-products, pork blood products, powder cellulose, hydrolyzed pork collagen, minerals, dried beet pulp, algal oil *Schizochytrium* sp., fish oil, psyllium husks and seeds, marigold meal		

Abbreviations: ME = metabolizable energy; NFE = nitrogen-free extract.

At UCPH and RVC, CBCs were performed using the same analyzer (ADVIA 2120i; Siemens Healthineers, Erlangen, Germany), but different analyzers were used for clinical chemistry (UCPH Atellica CH 930, Siemens Healthineers; RVC AU680, Beckman Coulter, Indiana, USA) and T4 (UCPH: Immulite 2000; RVC: Immulite 2000 XPi, both Siemens Healthineers). Fructosamine measurements were performed using the above clinical chemistry analyzers, except for 21/114 samples from UCPH that were analyzed at Idexx Laboratories (Vet Med labor GmbH, Ludwigsburg, Germany). Serum samples for fPLI and IGF-1 measurement were shipped on dry ice immediately after collection to Idexx Laboratories (Vet Med labor GmbH) or NationWide Laboratories (Cambridge, United Kingdom) for UCPH and RVC cats, respectively.

Measurement of blood glucose and glucose curves

Blood glucose (BG) concentrations were measured using a portable monitor (AlphaTrak 2; Zoetis, Kalamazoo, MI, United States), calibrated for use in cats.[34] Owners were taught how to use the glucometer and instructed to perform a 12 h blood glucose curves (BGC) at weeks 4, 8, and 12, and 1-2 weeks after any insulin dose adjustment. Principal investigators adjusted insulin doses based on clinical signs and BGC results (Table S5[35]). Owners were instructed to observe their cats for signs of hypoglycemia (eg, lethargy, weakness, ataxia). For cats in remission, owners were encouraged to continue spot BG measurements at least once weekly, and to monitor for signs of recurrence (eg, polyphagia, polyuria, polydipsia).

Assessment of clinical remission, glycemic control, weight reduction, and safety

The primary outcome measure was occurrence of diabetic remission, defined as either (a) normal serum fructosamine concentration (6.31 mg/dL [<350 μmol/L]) or BG concentration within the normal range (135 mg/dL [<7.5 mmol/L]),[34] measured ≥28 days after withdrawal of insulin[24] or (b) discontinued insulin treatment for at least 3 months and absence of clinical signs associated with DM. The date of remission was the day that insulin had been discontinued before the above criteria being recorded. Secondary outcome measures were assessments of glycemic control (eg, clinical signs related to DM according to DCS, insulin dose, serum fructosamine concentration, and glycemic variability [GV] calculated as the SD of BGC readings), QoL, percentage weight loss, and occurrence of harms or study withdrawals. All primary and secondary outcome measures were pre-determined and did not change during the study.

Safety assessments and study harms

Abnormal physical examination findings, clinically relevant laboratory abnormalities, or other relevant clinical observations were recorded as adverse events. Hypoglycemic events, diabetic ketoacidosis (DKA), hepatic lipidosis, progression of chronic kidney disease (CKD), and pancreatic status all were recorded as adverse events of special interest. Hypoglycemic events were categorized as non-clinical (BG <3.5 mmol/L [63 mg/dL], no clinical signs of hypoglycemia) or clinical (BG <3.5 mmol/L and hypoglycemic signs; eg, ataxia, lethargy, tremors, seizures). In clinically ill diabetic cats (eg, lethargy, anorexia, weight loss, vomiting, icterus), DKA was diagnosed based on the ALIVE criteria.[24] Hepatic lipidosis was suspected in ill anorectic cats with increased hepatic enzyme activity.[36] Progression of CKD was determined based on changes in creatinine, urea, phosphate, potassium, and symmetric dimethylarginine concentrations according to International Renal Interest Society (IRIS) guidelines.[37] Pancreatitis was suspected based on serum fPLI concentration [≥5.4 μg/L], and concomitant clinical signs. Cats in need of treatment because of severe clinical signs of illness were withdrawn from the trial.

Sample size

A sample size calculation, using a Kaplan–Meier survival curve model (R packages npsurvSS, powerSurvEpi),[38] determined that 76 cats would be sufficient to detect a significant group difference, assuming 1:1 assignment and 4 months remission rates of 70% and 45% in treatment and control groups, respectively. To fulfill model requirements, the following assumptions were made: recruitment time: 18 months; follow-up time: 6 months; follow-up of losses for other reasons (including death): 60 months. Assuming approximately 20% cats were lost to follow up, the final sample size was adjusted to 92 cats (46 caloric restriction, 46 controls).

Partly due to COVID restrictions, initial recruitment was slower than expected and 3 changes to the protocol were made: first, the recruitment period was extended to January 31, 2023; second, the acceptable duration of the cat having been diabetic before enrollment was extended from 6 to 24 months; and third, cats previously in remission but having subsequently relapsed for ≥4 weeks also were eligible for enrollment.

Clinical audit of diagnosis and clinical remission in study cats

Two European Board of Veterinary Specialization in internal medicine (AJG and Federico Fracassi, University of Bologna, Bologna, Italy), who were not involved in case recruitment or trial execution and were blinded to treatment allocation undertook an audit of all enrolled cats to confirm that recruitment of study cats had complied with the eligibility criteria and to evaluate clinical remission status. This audit involved a review of relevant anonymized clinical information including history and physical examination findings, laboratory results, BGC, insulin doses and dates of insulin discontinuation.

Although the initial duration for PZI treatment was set at 28 days, 4 cats had inadvertently started the study prematurely (ie, after 21-26 days of treatment). Before auditor unblinding, it was agreed that these cats could remain in the study because this situation would be unlikely to affect outcomes. Furthermore, auditor blinding was inadvertently compromised for 1 cat during this review. Given that it was the only error of its kind, it was again agreed that the cat could remain in the study.

Statistical methods

Data were analyzed using an open access statistical environment and language (R version 4.4.1, 2024-06-14[39]) and additional packages including: nlme, lme4, coxme, survminer, ggplot2, survival, lmerTest, dplyr, tidyr, emmeans, ordinal, and effectsize.[40–51] Numerical data are presented as median (range), or as number of cats and percentages. Normality was assessed using QQ-plots and appropriate normality tests. Pairwise comparisons of continuous variables (eg, age, body weight, duration of diabetes, glycemic variability) at baseline were undertaken using Mann–Whitney tests, whereas Fisher's exact test was used for comparisons involving categorical data. In statistical analyses, caloric allocations were expressed as kcal/kg $BW^{0.75}$ to enable direct between group comparisons.

Trial data was analyzed using the intention-to-treat (ITT) principle,[22,23] meaning that cats were analyzed in the groups to which they were originally randomized, regardless of whether they completed the trial. For cats withdrawn early, the "last observation carried forward" principle was used (eg, clinical status [remission or non-remission] remained unchanged from that observed at withdrawal).

Kaplan–Meier curves were created to estimate the distribution of time to remission (discontinuation of insulin) during the 12-week intervention period, whereas Cox's proportional hazards regression was used to identify variables associated with remission. Variables tested separately included: duration of DM, age, sex, BW change (at weeks 4, 8, and 12), caloric allocation (at weeks 0, 4, 8, and 12) and the percentage of daily calories provided from wet food (at weeks 0, 4, 8, and 12). Hazard ratios (HRs) and 95% CIs were calculated for all variables. Details for model diagnostics can be found in the supplementary information.

Linear mixed-effects models (LMM), with individual cat as random variable, were used to assess evolution and changes from baseline in each of the following variables: BW, fructosamine, biochemical analytes, insulin dose, and log-transformed glycemic variability (GV). Mean blood glucose concentration was calculated from BGCs (with ≥4 measurements) undertaken at revisits, with the SD used as a marker of GV. To avoid bias in analyses involving GV and insulin dose, data from cats in remission were excluded. Details for model diagnostics can be found in the supplementary information.

Cumulative link mixed models (CLMMs) were used to analyze ordinal data (eg, BCS, MCS, DCS). Model assumptions tested included the proportional odds ratio and the likelihood ratio test of random effects. Marginal estimates and 95% CI were calculated for the LMMs and CLMMs using emmeans.

Pre-determined subgroup analyses were performed for cats continuing to be insulin dependent to evaluate treatment effects in cats that did not achieve remission. Additionally, the DCS excluding appetite was evaluated to assess the role of appetite on the total DCS score in overweight cats undergoing weight reduction.

Average weighted impact score (AWIS), as well as questions QA and QB from the DIAQoL tool (Table S3)[27] were used to evaluate the impact of glycemic control on QoL changes in diabetic cats and their owners. A linear mixed effects model was used to assess changes in AWIS, whereas CLMMs were used for questions QA and QB. The threshold for statistical significance was set at $P < .05$. For the secondary outcomes, a false discovery rate (FDR) correction was performed, with a corrected $P < .05$ considered to be significant (Table S7). Results are presented as median (range) or marginal estimates (95% CI).

Results

Study samples

Owners of 86 cats initially were screened by telephone and, of these, 74 cats were randomized. However, 2 cats in the intervention group were excluded during case audit for not meeting eligibility criteria. Ultimately, 72 cats were included in the ITT analysis (intervention, 32; control, 40; Figure 1), with 29 recruited at UCPH and 43 at RVC. Baseline variables are shown in Table 3.

At enrollment, no differences were found between groups for age, sex, breed, BW, BCS, MCS, total insulin dose, and duration

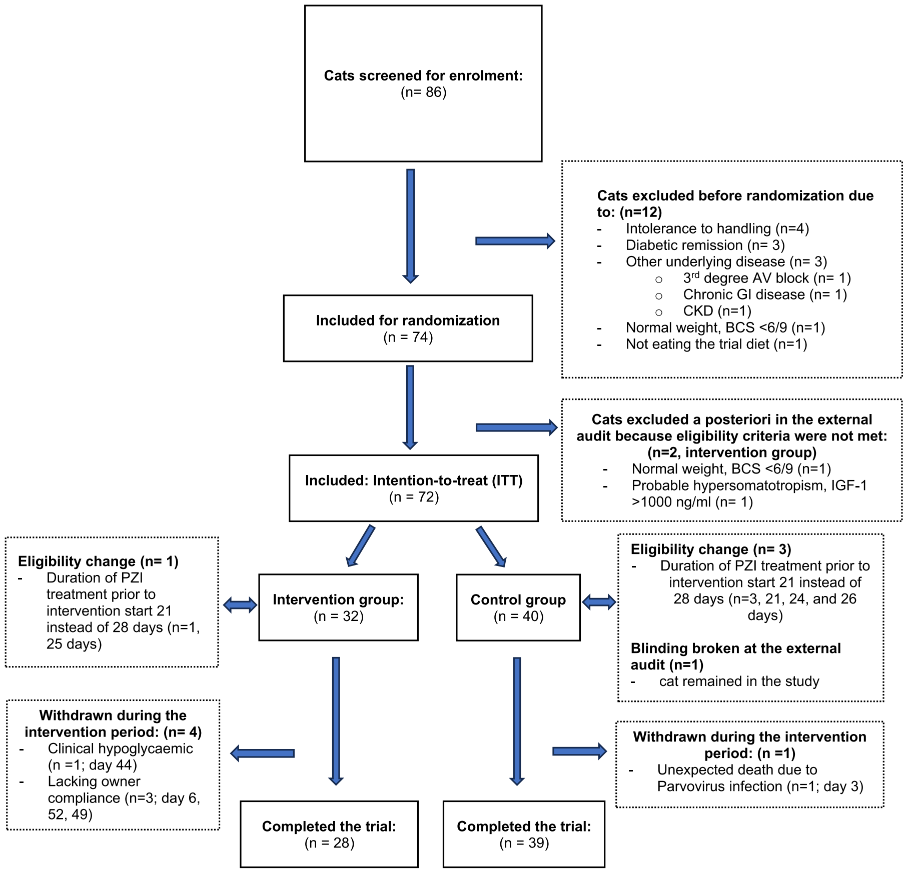

Figure 1 Details of the eligibility criteria and selection of final study group. Textboxes with a solid outline show the stage of the recruitment and study process, whereas those with a dotted outline indicate numbers of cats removed at each stage and the reason.

of DM. However, median GV was lower in control compared with intervention cats (*P* = .01; Table 3; Figure S2).

Primary outcome measure: remission status

In the ITT analysis, 28 cats had entered diabetic remission by week 12, with more in the intervention (16/32, 50%) than in the control (12/40; 30%; *P* = .05; Figure 2) groups. In the per-protocol analyses, remission was achieved in 16/28 (57%) and 12/39 (31%) of the cats in the intervention and control groups, respectively.

Secondary outcome measures

Measures of glycemic control

Serum fructosamine concentration improved over time ($P < .001$; FDR-corrected *P*-value $<.001$; Figure 3A; Table S6), with no difference between groups.

In cats remaining insulin-dependent, insulin dose decreased by 36% (95% CI, 2-70) in the intervention group, but increased by 28% (95% CI, 3-53) in the control group (*P* = .004; FDR-corrected *P* value = .02, Table S6, Figure 3B). Glycemic variability also decreased more in the intervention (45%; 95% CI, 26-65) compared with the control (7%; 95% CI, −21 to 16) groups (*P* = .01; FDR-corrected *P*-value = .04; Table S6; Figure 3C; Figure S2).

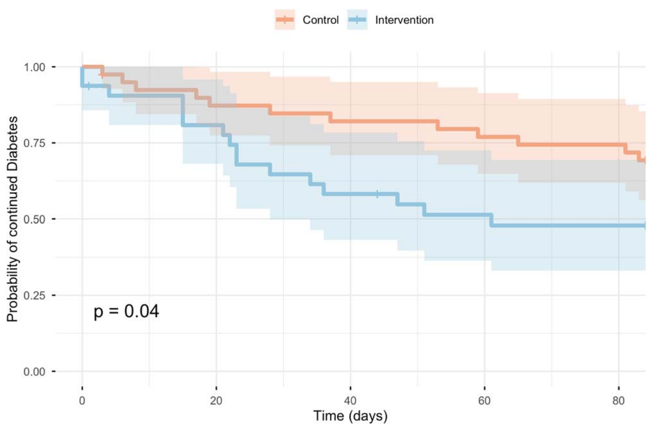

Figure 2 Kaplan–Meier estimate showing the distribution of time to remission (discontinuation of insulin) in a 12-week intervention period for overweight (BCS $\geq$ 6/9) cats fed calorie restricted (intervention, *n* = 32, blue line) or for maintenance (control, *n* = 40, red line). Shaded areas represent 95% CIs for each curve.

Body weight, body condition score, and muscle condition score

At the end of the intervention (week 12), calorie allocation (based on current BW) was 42 kcal/BW$^{0.75}$ (range, 32-60 kcal/BW$^{0.75}$) and 67 kcal/BW$^{0.75}$ (range, 45-84 kcal/BW$^{0.75}$) for the intervention and

Table 3 Characteristics of insulin-treated overweight diabetic cats at inclusion.

Variable	All cats	Intervention	Control	*P*-value
Number of cats	72	32	40	
Age (years)	11 [3-18]	10 [5-18]	11 [3-16]	.70
BW (kg)	6 [4.1-10.7]	5.8 [4.1-8.7]	6 [4.4-10.7]	.76
Sex				.14
Neutered male	47 (65%)	24 (75%)	23 (58%)	
Neutered female	25 (35%)	8 (25%)	17 (43%)	
Breed				.30
Domestic short hair	55 (76%)	26 (81%)	29 (73%)	
Domestic long hair	10 (14%)	5 (16%)	5 (13%)	
Other breeds	7 (10%)	1 (3%) Burmese (1)	6 (15%) British shorthair (1) Maine Coon (2) Norwegian Forest cat (1) Ragdoll (1) Siberian Forest cat (1)	
BCS				.66
6/9	16 (22%)	5 (16%)	11 (28%)	
7/9	34 (47%)	17 (53%)	17 (43%)	
8/9	15 (21%)	7 (22%)	8 (20%)	
9/9	7 (10%)	3 (9%)	4 (10%)	
MCS				.79
A	34 (47%)	17 (53%)	17 (43%)	
B	28 (39%)	11 (34%)	17 (43%)	
C	9 (13%)	4 (13%)	5 (13%)	
D	1 (1%)	0 (0%)	1 (3%)	
Duration of DM (days)	131 [24-977]	105 [31-977]	153 [24 -925]	.18
Total daily insulin dose	3.25 [1-10]	4 [2-10]	3 [1-10]	.46
Glycemic variability	3.7 [0.6-11.4]	4.7 [0.6-8.3]	3.1 [0.7-11.4]	**.01***

Number of cats was 32 (intervention: caloric restriction) and 40 (control: maintenance, except for glycemic variability (intervention, 28; control, 37). Results are reported as median [range] or number (percentage). *P*-values are reported for comparisons between groups. Glycemic variability was calculated as the standard deviation [SD] of BGC readings. Abbreviations: BW = body weight; BCS = body condition score; MCS = muscle condition score.

control groups, respectively. The intervention group lost 7.2% (95% CI, 5.7-8.7) of initial BW, compared with 2.7% (95% CI, −4.1 to 1.3) in the control group ($P < .001$; FDR-corrected *P*-value $< .001$; Table 4 and Table S6). Body condition score decreased more in intervention compared with control cats ($P = .01$; FDR-corrected *P*-value = .01; Table 4 and Table S6), but no difference was found in MCS between groups ($P = .18$, FDR-corrected *P*-value = .3; Table 4 and Table S6).

Diabetic clinical score and quality of life

The DCS improved during the 12-week period ($P < .001$; FDR-corrected *P*-value $< .001$, Table S6; Figure 4A) with no difference between groups ($P = .28$; FDR-corrected *P*-value = .47; Figure 4A; Table S6).

The DCS data were re-analyzed, excluding appetite, because of the potential confounding effect from caloric restriction and to allow a clearer assessment of clinical signs independent of appetite. More improvement in cats from the intervention group occurred compared with controls ($P = .003$; FDR-corrected *P*-value = .01; Table S6; Figure 4B). The DIAQoL-pet improved during the 12-week intervention with no difference between groups (Table 5). Time-dependent, but not group-related improvements also were observed in AWIS (−2.3; 95% CI, −2.0 to −2.7; $P < .001$; FDR-corrected *P*-value $< .001$), question A (QA; 3.9; 95% CI, 2.9-4.8; $P < .001$; FDR-corrected *P*-value $< .001$), and question B (QB; −2.1; 95% CI, −1.3 to −3.0; $P < .001$; FDR-corrected *P*-value $< .001$; Table 5 and Table S6).

Variables associated with diabetic remission

Using Cox's proportional hazards regression, the likelihood of achieving diabetic remission was 2.1 times higher in intervention as compared with control cats (Table 6, 95% CI, 1.0-4.51; $P = .05$), with 13/16 and 7/12 cats achieving remission within 6 weeks, in the intervention and control groups, respectively. Furthermore, caloric restriction implemented at weeks 0 and 4 significantly increased the likelihood of achieving remission by week 12 (Table 6; Figure 5).

At week 4, cats fed 40 kcal per kg $BW^{0.75}$ per day were predicted to have 4.3 times higher likelihood of achieving diabetic remission compared with cats fed 80 kcal per kg $BW^{0.75}$ per day calculated using current BW (Figure 5; Table 6). Furthermore, a shorter duration of DM before study enrollment was positively associated with diabetic remission (Table 6; Figure S3) compared with having previously had DM for 600 days. Cats having DM for 30 days or 200 days had 6.9 times and 3.9 times the likelihood of entering remission, respectively. However, age, sex, BW change during the intervention and proportion of wet diet did not affect likelihood of achieving remission (Table 6).

Table 4 Changes in bodyweight, body condition and muscle condition during a 12-week dietary intervention in overweight diabetic cats.

Variable	Visit	Intervention		Control	
		Number	Median (range)	Number	Median (range)
Bodyweight	Week −1	32	5.8 (4.1-8.7)	40	6 (4.4-10.7)
	Week 12	26	5.3 (3.6-7.2)	39	5.7 (4.1-9.2)
BCS	Week −1	32	7 (6-9)	32	7 (6-9)
	Week 12	26	6 (5-8)	26	7 (5-9)
MCS	Week −1	32	A (A-C)	32	B (A-D)
	Week 12	26	B (A-C)	26	A (A-C)

Intervention: caloric restriction; control: maintenance. Abbreviations: BCS = body condition score; MCS = muscle condition score. Results are shown as median [range].

Table 5 Results of average-weighted impact score and questions from the diabetes-dependent quality (DIAQoL-Pet) of life questionnaire in study cats.

Variable	Visit	Intervention		Control	
		Number	Median (range)	Number	Median (range)
AWIS	W−1	28	−3.3 (−8.1 to −1.52)	37	−3.5 (−5.7 to −0.8)
	W12	20	−1.8 (−5.1 to −0.2)	33	−2.4 (−5.7 to −0.3)
QA	W−1	28	8 (4-10)	37	8 (5-10)
	W12	20	9 (1-10)	33	8 (5-10)
QB	W−1	28	2 (1-3)	37	2 (0-3)
	W12	20	1 (−1 to 3)	33	1 (−2 to 3)

A single quantitative measure of diabetes-dependent QoL, average-weighted impact score (AWIS) was derived by averaging all item-weighted impact scores (IWIS) across 29 items. Most items represented areas in the owner's and pet's lives that diabetes could negatively impact, with frequency scores ranging from −3 to 0. In contrast, 3 items in the diabetes-dependent quality of life questionnaire (DIAQoL-pet) addressed potential positive effects and were assigned frequency scores between 0 and 3. DIAQoL-pet question A (QA) and B (QB) during the 12-week intervention period for the intervention and control group. QA: "I feel that the quality of life of my pet's life is": Score 1-10. QB: "If your pet did not have diabetes, his/her quality of life would be": Score 3 = Much better; score 2 = better; score 1 = a little better; score 0 = the same; score −1 = a little worse; score −2 = worse; score −3 = much worse.[27]

Study withdrawals and harms

No cats developed DKA or hepatic lipidosis during the study, but 9 adverse events occurred, 2 of which resulted in withdrawal (Figure 1). Adverse events in the intervention group were non-clinical hypoglycemia (4 cats), clinical hypoglycemia (1 cat, euthanized on day 44 upon owner request), whereas those in the control group had non-clinical hypoglycemia (3 cats) and progression of CKD (1 cat; increased serum creatinine concentration week −1: 1.28 mg/dL [113 μmol/L]; week 12: 1.63 mg/dL [144 μmol/L]. One control cat was withdrawn (day 3) because of parvovirus infection, an event not considered related to the trial. No hematology or biochemical abnormalities were identified during the study, including hepatic, pancreatic, or renal analytes. Finally, three intervention group cats were withdrawn prematurely (at 6, 52, and 49 days) because of poor owner compliance, including inability to feed the trial diet exclusively or to attend scheduled follow-up visits.

Discussion

In our study, 12 weeks of caloric restriction using a diabetic diet formulated for weight reduction, more than doubled the likelihood of achieving remission in overweight diabetic cats. Furthermore, glycemic control improved, as evidenced by decreased insulin doses, decreased GV, decreased serum fructosamine concentration and improvements in both DCS and DiaQoL. Despite the ability of caloric restriction in humans to introduce diabetic remission,[52] no previous studies have assessed therapeutic weight reduction in overweight diabetic cats,[34] and currently, few therapeutic diabetic diets designed for weight reduction are available. Interestingly, remission was more closely associated with degree of caloric restriction than weight lost, with the likelihood of remission being 4 times higher for cats fed 40 kcal/BW$^{0.75}$ compared with 80 kcal/BW$^{0.75}$ using current BW. Indeed, most (13/16) intervention cats entering remission did so within the first 6 weeks. Therefore, when inducing remission, rather than focusing on weight loss, clinicians should aim to calculate an accurate, calorically-restricted food portion, and counsel owners to adhere to feeding this amount. By the end of the trial, intervention groups cats were fed 42 kcal/BW$^{0.75}$/day, equivalent to 119 kcal/day for a 4 kg cat or 63% of MER, which aligns well with current recommendations for therapeutic weight reduction.[53] At such intakes, a diet designed for weight maintenance (including standard therapeutic diets for diabetic cats) would not be suitable given potential essential nutrient deficiencies.[54] The increased nutrient:energy ratio in the study diet, adequately addresses this concern.

In humans, weight loss induced by energy restriction improves glycemic control and promotes diabetic remission.[18–21,52,55–57] The acute negative energy balance decreases pancreatic and hepatic lipid accumulation, possibly mediated by decreased circulating fatty acid concentrations and normalization of both β-cell function and hepatic glucose output.[58,59] In humans, caloric

Table 6 Cox's proportional-hazards regression of covariables associated with remission in overweight diabetic cats during a 12-week dietary intervention.

Variable	Number	Hazard ratio	95% CI	*P*-value	Adjusted *P* (FDR)
Intervention vs. control	72	2.13	1.00-4.51	**.05***	-
Covariables [a]					
Duration of DM (per 100 days)	72	1.40	1.04-1.86	**.02***	**.05***
Age (years)	72	0.93	0.82-1.04	.2	.2
Sex	72				
Male		2.04	0.82-5.11	.12	.12
Bodyweight change (%)					
Week 4	68	1.04	0.93-1.15	.52	.65
Week 8	64	1.01	0.93-1.09	.83	.83
Week 12	65	0.98	0.90-1.06	.54	.65
Caloric allocation (40 kcal/BW $^{0.75}$) [a]					
Week 0	72	3.26	1.01-9.66	**.05**	**.05**
Week 4	68	4.28	1.22-13.30	**.02**	**.04**
Week 8	64	2.67	0.85-8.17	.08	.09
Week 12	66	2.58	0.85-7.36	.09	.09
Energy from wet food (%)					
Week 0	72	1.00	0.99-1.01	.68	.94
Week 4	68	1.00	0.99-1.01	.89	.94
Week 8	64	1.00	0.99-1.01	.94	.94
Week 12	66	1.00	0.99-1.01	.94	.94

Abbreviations: BW = body weight; FDR = false discovery rate; n = number of cats; *P*, *P*-value; -, not included in the model. FDR was calculated for secondary outcomes to control the risk of false positive findings. [a] Most covariates (eg, duration of diabetes, age, sex, bodyweight change, and energy from wet food) were analyzed as continuous or categorical variables without comparison to a fixed reference value. The continuous covariate caloric allocation with the unit (per *40 kcal/kg BW^{0}*)[74], allowing estimation of its predictive value for diabetic remission.

restriction alone also induces metabolic improvements, even before weight loss occurs,[58] consistent with our results where weight loss rate was not associated with diabetic remission. However, the exact mechanisms through which caloric restriction promotes diabetic remission are not fully understood either in humans or cats.[52]

To date, the priority for dietary management of DM in cats is optimizing glycemic control by prioritizing endogenous glucose production, thereby minimizing postprandial glucose influx,[34] achieved by substituting dietary carbohydrate with protein or fat. The optimal carbohydrate content in therapeutic diets for diabetic cats is unknown, but a content of $<$12% ME is suggested,[34,60] albeit without validation in clinical trials. Given that we only tested a single diet, our results cannot address the question of optimal carbohydrate content for diabetic cats, but the percentage of wet food consumed did not affect the likelihood of remission, in contrast to a previous study.[14] Furthermore, improved glycemic regulation was observed in both the intervention and control groups, despite the NFE content of the dry diet being 27% ME. Therefore, the improved glycemic control observed might instead be related to other diet characteristics, such as high protein, low fat, or low starch contents.

In our study, the target of 2%/week weight loss rate was not consistently met, with the rate ultimately achieved (0.6%/week) being similar to previous studies assessing weight reduction in overweight cats without DM.[61,62] This result perhaps represents a physiologically-realistic and achievable rate in pet cats, especially when their owners have to confront increased food-seeking behavior.[61]

Besides a possible increased frequency of hypoglycemic episodes, adverse events were uncommon in both study groups, and this observation is similar to studies of caloric restriction in human diabetics.[52] In our study, 1 cat (intervention) suffered from clinical hypoglycemia, which resulted in euthanasia, whereas non-clinical hypoglycemic episodes were reported in 7 other cats (4 intervention, 3 control). These results are comparable with the incidence of hypoglycemia in PZI-treated diabetic cats not undergoing caloric restriction.[12,63,64] Serum markers of hepatic, pancreatic, and renal function remained stable during the study, with no group differences. Therefore, caloric restriction can be safely implemented in overweight diabetic cats under veterinary supervision.

Although DCS improved in both groups, improvement was larger in the intervention group when appetite was excluded from the assessment. Whether increased appetite score reflects increased food-seeking, resulting from caloric restriction, or polyphagia, caused by underlying DM, is unknown. Increased food-seeking behavior usually is observed in cats undergoing therapeutic weight reduction,[65,66] albeit not in a recent multicenter study where owners instead reported decreased food-seeking behavior.[62] Given that increased food-seeking behavior might not solely reflect poor diabetic control, owners and clinicians

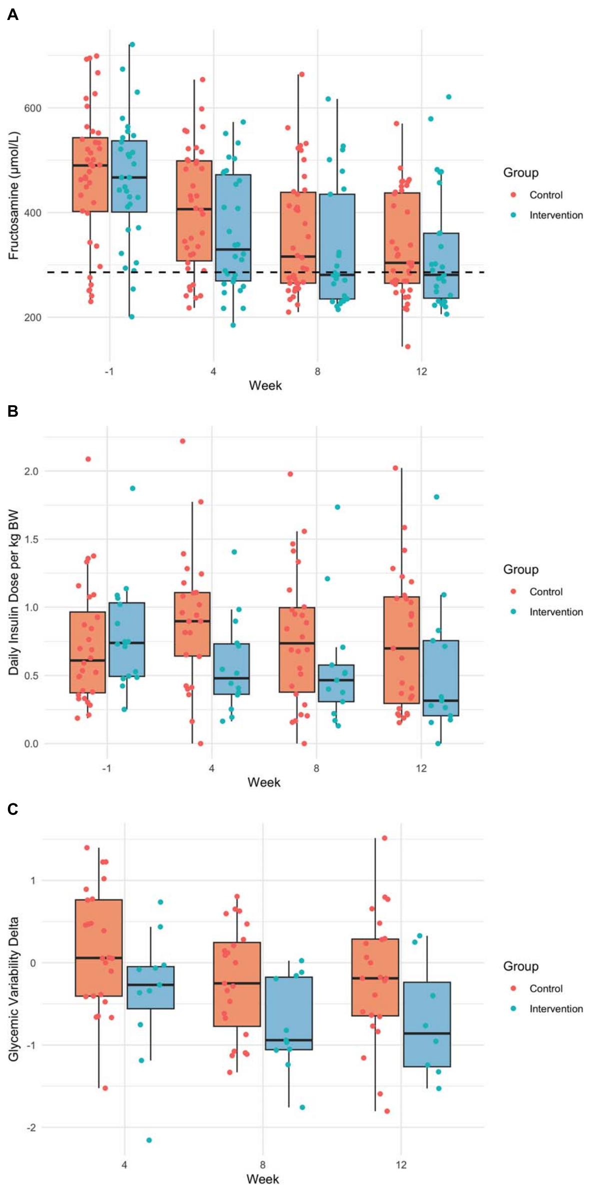

Figure 3 (A) Fructosamine concentration during a 12-week dietary intervention in overweight diabetic cats. Values are presented at each time point for the intervention (calorie-restricted) and control groups respectively: week −1 (intervention, $n = 32$; control, $n = 40$, week 4 (intervention, $n = 30$; control $n = 38$), week 8 (intervention, $n = 25$; control, $n = 38$), and week 12 (intervention, $n = 27$; control, $n = 39$). The red line represents the upper reference interval (286 μmol/L). (B) Daily insulin dose per kg BW for the cats not obtaining remission in the 12-week intervention. Week −1 (intervention, $n = 16$; control, $n = 28$, week 4 (intervention, $n = 15$; control $n = 27$), week 8 (intervention, $n = 13$; control, $n = 26$), and week 12 (intervention, $n = 13$; control, $n = 27$). (C) Change in glycemic variability (GV) for overweight diabetic cats not obtaining remission in a 12-week intervention period. Week 4 (intervention, $n = 11$; control, $n = 24$, week 8 (intervention, $n = 11$; control, $n = 23$), and week 12 (intervention, $n = 8$; control, $n = 23$). For all figures, the thick horizontal black lines represent the median, the upper and lower limits of the boxes represent the inter-quartile range (IQR), and the whiskers extend as far as the largest or smallest values, respectively, that are $\leq$ 1.5 times the IQR. The individual dots represent results, at different time points, for each cat in the intervention (caloric restriction; blue) and control (maintenance; red) groups, respectively.

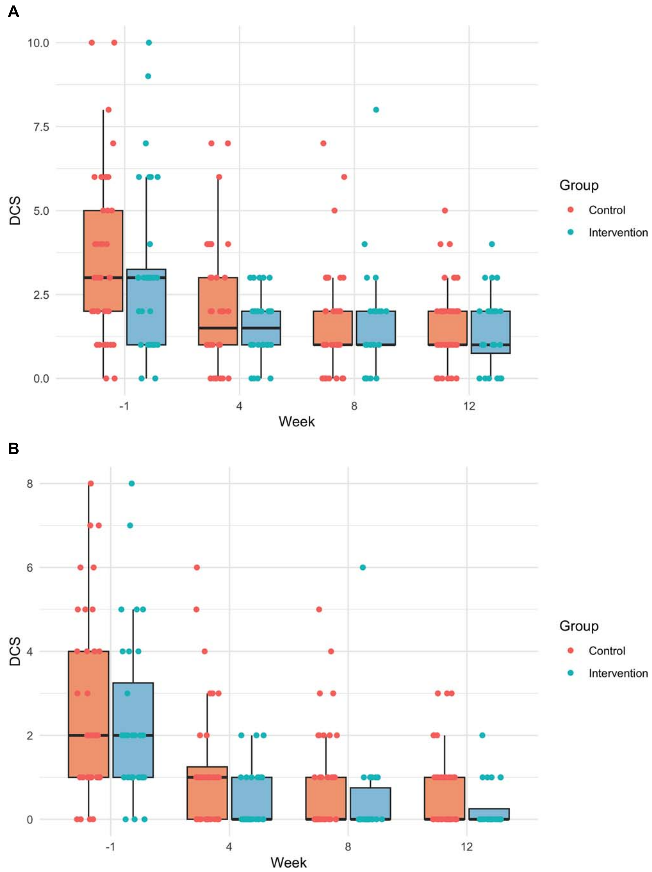

Figure 4 Combined box-and-whisker and dot plots comparing (A) diabetic clinical score (DCS) and (B) DCS excluding the appetite question during the 12-week intervention. In each figure, thick horizontal black lines represent the median, the upper and lower limits of the boxes represent the inter-quartile range (IQR), and the whiskers extend as far as the largest or smallest values, respectively, that are $\leq$1.5 times the IQR. The individual dots represent results, at different time points, for each cat in the intervention (caloric restriction; blue) and control (maintenance; red) groups, respectively. The number of cats at each time point were 32 (intervention) and 38 (control) at week −1; 30 (intervention) and 36 (control) at week 4; 26 (intervention) and 37 (control) at week 8; and 24 (intervention) and 38 (control) at week 12.

should exercise caution when interpreting appetite in overweight diabetic cats undergoing weight reduction.

Quality of life improved in both groups during the study, consistent with other studies where improved QoL was associated with close monitoring and diabetic remission.[14,67] Finally, consistent with a previous study, a shorter duration of diabetes was associated with a higher chance of achieving diabetic remission.[13] Newly diagnosed cats may present with a BCS 3-5/9 caused by weight loss. We do not recommend caloric restriction and further weight loss in these specific cases, where the veterinarian should focus on achieving glycemic control and stabilizing BW medically and nutritionally. In case of subsequent weight gain above BCS 5-6/9, caloric restriction should be considered.

Our study had several limitations. First, we included 4 cats (2 intervention; 2 control) that had previously been in remission, which might have affected outcomes given that re-entering remission would be less likely,[68] as proved to be the case for these cats. Second, blinding was not feasible either for the primary

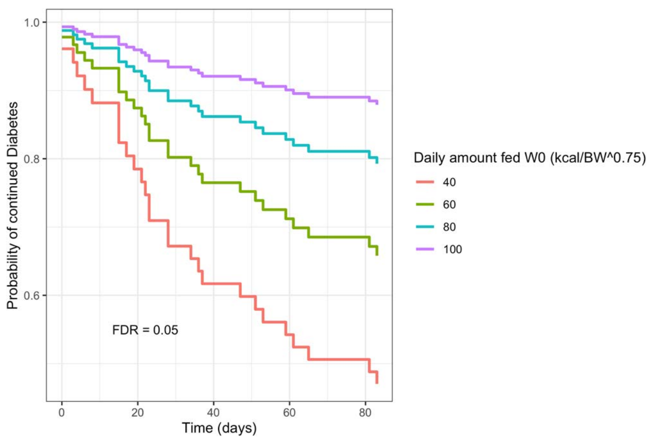

Figure 5 Results of Cox's proportional-hazards analysis showing calorie allocation at week 0, predicting the risk for a cat having diabetes mellitus (eg, continuing to need insulin treatment) at any time point (days) during the 12-week intervention phase for a cat on different calorie allocations. The different lines represent groups of cats with the following model average caloric allocations: 100 kcal (purple), 80 kcal (blue), 60 kcal (green) and 40 kcal (red) per $kg^{0.75}$ of body weight. Caloric allocation was expressed as kcal/kg $BW^{0.75}$ for all cats (n = 72) for comparison irrespective of group. Please note that for clarity, 95% CIs have not been included. FDR: *P*-value corrected for the false-discovery rate using the Benjamini–Hochberg method.

study investigators or the cat owners, because group allocation (caloric restriction vs control) could easily be deduced from the feeding instructions. Such unblinded clinical trials can be subject to bias. For example, owner expectations might influence reporting of clinical signs or improvement, whereas clinicians might unconsciously alter the care provided (eg, better supporting owners of cats in a favored treatment group[69]). In unblinded studies, attrition is typically higher among participants in the control group.[70] The fact that this difference did not occur in our study might suggest that equal support was given to owners in both groups. Indeed, all compliance-related withdrawals were from the intervention group, possibly reflecting the greater challenge of implementing and adhering to dietary restriction.

Third, regarding randomization, unequal numbers of cats were enrolled in each group, with 32 and 40 cats in the intervention and control groups, respectively. This imbalance might have been the result of using a simple randomization protocol, where such discrepancies are not uncommon, especially in studies involving $<$200 subjects.[71] This discrepancy might have been minimized if block randomization had been used. That said, the difference between groups is within that expected for a study of this size and reflects the inherent nature of randomness.[71] Fourth, bias might have been introduced by having 2 study sites. We addressed this concern by conducting sensitivity analyses, whereby Cox's regression models were repeated after stratification by study site. Given similar results, the unstratified analyses were used for final models.

Finally, although reaching and maintaining diabetic remission is desirable in diabetic cats, approximately 25%-30% will subsequently relapse.[60,72,73] In a recent study, involving exenatide extended-release insulin, $>$50% of diabetic cats remained in remission for $>$2 years regardless of treatment.[74] Therefore, with frequent monitoring, regular nutritional support, and a focus on achieving and maintaining ideal BCS, prolonged diabetic remission should be feasible.

Conclusion

A short period of controlled caloric restriction using a purpose-formulated diabetic diet is safe overall, and improves the likelihood of remission in overweight diabetic cats, while also improving glycemic control in those not achieving remission. The fact that remission was more closely associated with degree of caloric restriction than percentage weight loss suggests that veterinarians adopting such a strategy should prioritize accurate calculation of daily food allowance and ensure owner adherence to the feeding plan.

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Author contributions

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Supplementary material

Supplementary material is available at *Journal of Veterinary Internal Medicine* online.

Conflicts of interest

Royal Canin SAS, a division of Mars Petcare, manufactured the diets used in this study. Salaries for F.K.J., A.M., R.G., S.N., S.B., I.N.K., D.X., M.W., Tvd.W., and M.H.R. have been partly financed

by Royal Canin. C.R.B., R.G., and L.J.D. were PI's on the project and supervisors for the PhD students F.K.J. and A.M. CRB receives support for a clinical nutrition service at the University of Copenhagen from Royal Canin Denmark and has also received financial remuneration for speaking at conferences and symposiums, and consultancy work unrelated to the current study from Royal Canin, Boehringer Ingelheim, Hills and E-Vet. R.G. has received consultancy work and speaker honorariums from Royal Canin and Boehringer Ingelheim. L.J.D. is in receipt of additional grant funding for projects unrelated to this study and has received financial renumeration for consultancy work from Royal Canin and for speaking at conferences unrelated to the current study. A.J.G. is an employee of the University of Liverpool, but his position is financially supported by Royal Canin. A.J.G. has also received financial remuneration and gifts for providing educational material, speaking at conferences, and consultancy work, all unrelated to the current study. J.F. and T.H. are employees of Royal Canin, Aimargues, France.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Off-label antimicrobial declaration

Authors declare no off-label use of antimicrobials.

Institutional animal care and use committee or other approval declaration

The study protocol was approved by the local ethics committee at the Department of Veterinary Clinical Sciences, University of Copenhagen (Approval No. 2021-2); the Clinical Research Ethical Review Board at the Royal Veterinary College, United Kingdom (Approval No. URN 2020 2020-3); and Royal Canin's Ethical Review Committee, Aimargues, France (approval No. 250820-34).

Human ethics approval declaration

Authors declare human ethics approval was not needed.

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