Title page:

Pilot study assessing the use of cabergoline for the treatment of cats with hypersomatotropism and diabetes mellitus

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Abstract

Objectives: An affordable and effective treatment is needed to manage feline hypersomatotropism ~~/ acromegaly~~. The study aim was to assess whether treatment with oral cabergoline for 90 days in cats with hypersomatotropism and diabetes mellitus improves diabetic and insulin-like growth factor 1 control.

Methods: Prospective cohort non-blinded pilot study enrolling client owned cats with spontaneously occurring diabetes mellitus and hypersomatotropism. Cats received oral cabergoline (5 to 10 µg/kg q24 h) for 90 consecutive days. Serum insulin-like growth factor 1 and fructosamine concentrations were measured on days 1, ~~5~~, 30 and 90. Quality of life was determined using the DIAQoL-pet questionnaire on days 1 and 90.

Results: Nine cats were enrolled and eight completed the study. There was no significant change of insulin-like growth factor 1 (day 1 median was 2001 [range 890 to 2001]; day 30 median was 2001 [range 929 to 2001]; day 90 median was 1828 [range 1035 to 2001] ng/mL ($X^2(2) = 0.667$, $P = 0.805$), fructosamine (day 1 median was 499 [range 330 to 887], day 30 median was 551 [range 288 to 722], day 90 median was 503 [range 315 to 851] µmol/L, $X^2(2) = 0.581$, $P = 0.764$), or DIAQoL-pet score (median on day 1 was -2.79 [range -4.62 to – 0.28], median on day 90 was -3.24 [range -4.41 to -0.28], $P = 0.715$). There was a significant change of insulin dose ($X^2(2) = 8.667$, $P = 0.008$) with cats receiving higher insulin doses at day 90 compared to day 1 (median day 1 was

0.98 [range 0.63 to 1.49] and median day 90 was 1.56 [range 0.49 to 2.55] units/kg q12h, P = 0.026.

Conclusions and relevance: Cabergoline did not improve diabetic or normalise insulin-like growth factor concentration, nor improve patient quality of life.

Introduction:

Hypersomatotropism (HST) in cats is a condition caused by chronic excessive growth hormone (GH). Most cats with HST have concurrent diabetes mellitus (DM) which can be difficult to control using treatments which only target glycemic control.

Medical management using pasireotide or surgical management via hypophysectomy has improved GH and diabetic control in cats with HST.[1–3] However, these treatments are often too costly for owners and effective alternative modalities are needed.

In human medicine, HST is known as acromegaly due to the phenotypic changes induced by the condition. There are three main medical management options for acromegaly in humans which are somatostatin receptor agonists (SRAs) such as octreotide or pasireotide, dopamine receptor agonists (DRAs) such as bromocriptine or cabergoline and growth hormone receptor antagonists, namely

63 pegvisomant. Recommendations suggest the primary medical treatment of patients
64 who have moderate-to-severe disease should be SRAs and patients who have mild
65 disease (serum insulin-like growth factor 1 [IGF1] < 2 times the upper limit of the
66 age adjusted range) can be treated using a DRA.[4,5] The direct mechanism of action
67 of GH-secretion inhibition by DRAs is thought to be via somatotrope dopamine 2
68 receptors (D2Rs) within the pituitary.[6] As cats with HST have pituitary expression of
69 D2R, therapy with a DRA might result in improved GH control and therefore
70 diabetic control.[7]
71
72 Cabergoline and bromocriptine are DRAs with high affinity for D2R in rats and
73 monkeys[8,9]. Cabergoline is the D2R-specific DRA with more favourable properties,
74 having a longer action of duration and thus requires less frequent dosing, is better
75 tolerated and exhibits increased insulin sensitising effects independent of GH
76 reduction compared to bromocriptine.[10,11] An oral preparation of cabergoline was
77 licensed and available for use in cats at the time of study (Kelactin, Kela N.V.)
78 Cabergoline has also been proven to be well tolerated when administered for

several months in both dogs and humans.[12,13]

The aim of the pilot study was to determine if cats with HST and DM experienced decreased serum IGF1 and improved diabetic control determined by serum fructosamine concentration and insulin dose requirement when receiving once daily treatment with oral cabergoline. A secondary aim of the study was to determine whether this treatment resulted in improved quality of life of these cats.

Materials and methods

The study was approved by the Ethics and Welfare Committee of the Royal Veterinary College, UK; URN 2016 1604. Informed written consent was obtained from all owners before enrolment. Cats with HST were prospectively enrolled between 01/10/2016 and 31/05/2017. Inclusion criteria were DM which had been treated for at least four weeks prior to enrolment, serum IGF1 concentration >700 ng/mL with pituitary enlargement (>4mm dorsoventral height) or serum IGF1 >1000 ng/mL without pituitary imaging. Since IGF1 >1000 ng/mL has been shown

to have a positive predictive value for HST of 95% in the UK diabetic cat population where the prevalence of HST was 25%, necessity of additional pituitary imaging in this group was not deemed essential.[14] If contrast enhanced pituitary imaging had not already been performed and the owner consented to the procedure, then this was undertaken on day 1 as previously described.[15] Exclusion criteria were poor patient tolerance of veterinary procedures, uncontrolled hyperthyroidism, insulin antagonist therapy within the preceding four weeks prior to enrolment or if they had a disease which was more critical to the cat's welfare than HST as judged by the attending clinician.

Owners of eligible cats were offered a reduced fee for contrast enhanced CT of their cat, free supply of PZI insulin (Prozinc, Boehringer Ingelheim) and diabetic cat food (Purina DM, Nestle Purina) for the length of the study. Owners paid for the initial period of hospitalization and the cost of cabergoline during the study. Owners were encouraged to perform home blood glucose monitoring.

On day 1, a blood sample was collected for pre-treatment CBC, serum biochemistry, serum IGF1 and fructosamine concentration determination. Cats had a subcutaneous interstitial glucose monitor (Guardian REAL Time Continuous Glucose Monitoring System, Medtronic) placed to measure glycemic control for an initial period of hospitalization of four days[17]. Cats received the same insulin dose and frequency as prescribed by their referring veterinarian prior to enrolment on day 1, cats were prescribed oral cabergoline once daily starting on day 2 and were discharged on day 5. Cats were monitored for possible adverse drug effects, whether there was increased sensitivity to insulin therapy as determined by glycemic control during hospitalization, clinical sign monitoring by their owners and repeat fructosamine measurement on days 30 and 90, and IGF1 measurements were repeated on days 30 and 90 ~~(Figure 1)~~.

Patient quality of life (QoL) was assessed by requesting owners to complete the psychometric DIAQoL-pet questionnaire at day 1 and 90. The DIAQoL-pet has previously been validated to quantify owner perceived QoL of diabetic pet and

owner, and can quantify the effect of treatment upon their diabetic cat's quality of life as well as their own.[18]

Statistical Analysis

A P value < 0.05 was considered significant. Data were analysed for normal distribution visually using histograms and by performing Shapiro–Wilk tests. Any IGF1 concentration > 2000 ng/mL was analysed as being 2001 ng/mL. Non-normally distributed data are presented as median and range and data with normally distributed data presented as mean and standard deviation (S.D.). Friedman tests and post-hoc related samples Wilcoxon signed rank tests with Bonferroni adjustment where appropriate were performed to compare repeated measures IGF1, fructosamine and insulin dose data on days 1, 30 and 90. Related samples Wilcoxon signed rank test was used to compare QoL data on days 1 and 90. The Spearman rank test was used to compare the strength of correlation between data. Statistical analyses were performed using statistical software

(GraphPad Prism version 8.4.0 for macOS, GraphPad Software and IBM SPSS Statistics Version 26.0.0.0 for macOS, IBM Corp).

Results

Nine cats were enrolled, eight cats completed the study and one cat (cat 1) died during the study. The data from the cat which did not complete the study was excluded from these analyses of insulin dose, fructosamine, IGF1 and DIAQol-pet scores. All nine cats were DSH breed, six were male and three were female, the mean age was 10.8 years (S.D. 2.8), mean weight was 4.8 kg (S.D. 0.8), mean pituitary dorsoventral height was 6.3 mm (S.D. 1.6) and median pituitary volume was 0.088 cm^3 (range 0.048 to 0.327). Cat 6 did not undergo intracranial CT imaging because of the concern this patient had a high risk for congestive heart failure as determined by echocardiographic measurements. Home blood glucose monitoring was performed by 4/9 owners. All owners reported they were successful when giving cabergoline to their cats and that the medication had been handled per manufacturer's instructions.

The first three cats enrolled on the study received 5 µg/kg cabergoline q24h but had a dose increase to 10 µg/kg q24h at day 30 to 35, and the remaining cats had a cabergoline dose of 10 µg/kg q24h from enrolment. Cat 7 did not have IGF1 and fructosamine measurements at day 30.

Serum IGF1 results

There was no significant change of serum IGF1 concentration over the three months of the study (day 1 median was 2001 [range 890 to 2001]; day 30 median was 2001 [range 929 to 2001]; day 90 median was 1828 [range 1035 to 2001] ng/mL, $X^2(2) = 0.667$, $P = 0.805$) (Figure 1). Four experienced a decrease and four an increase IGF1 from day 1 to day 90. The median pituitary volume of cats which experienced IGF1 reduction was not significantly different to those who did not experience a reduction of IGF1 (0.086 vs and 0.133 cm^3, $P = 0.94$).

Serum fructosamine and insulin dose

There was no statistical difference of fructosamine concentration at any time point (day 1 median was 499 [range 330 to 887], day 30 median was 551 [range 288 to 722], day 90 median was 503 [range 315 to 851], $X^2(2) = 0.581$, $P = 0.764$) (Figure 2). An insulin dose increase was prescribed for 6/8 cats. There was a significant change of insulin dose prescribed during the study ($X^2(2) = 8.667$, $P = 0.008$), with cats receiving higher insulin doses on day 90 compared to day 1 (median day 1 was 0.98 [range 0.63 to 1.49] and median day 90 was 1.56 [range 0.49 to 2.55] units/kg q12h, $P = 0.026$.) (Figure 3).

DIAQol-pet scores

The DIAQol-pet was completed by 6/8 owners of cats. There was no statistical change of DIAQoL-pet scores between day 1 and day 90 (median on day 1 was -2.79 [range -4.62 to – 0.28], median on day 90 was -3.24 [range -4.41 to -0.28], $P = 0.715$), (Figure 4). DIAQoL-pet scores negatively correlated with insulin dose on day 1 but not on day 90 (Spearman's rank -0.871, $P = 0.034$ and -0.257, $P = 0.623$, respectively).

Potential adverse drug effects

One cat died during the study period (cat 1 in Supplemental Table 1). General physical examination at enrolment of this cat was unremarkable apart from a grade 2/6 systolic cardiac murmur. An echocardiogram was not performed at enrolment. On day 82, the cat developed tachypnoea and was diagnosed with supraventricular tachycardia and congestive heart failure. The cat's owners elected for him to be euthanized and a post-mortem examination was declined.

Cat 7 did not have fructosamine or IGF1 data for day 30 because he was hospitalized at his local veterinary practice for an episode of presumed pancreatitis on day 28. Cat 5 experiencing reduced appetite and small intestinal diarrhea which resolved within one week without specific treatment, and the same cat experienced asymptomatic hypoglycemia on day 60. Two other cats experienced self-limiting inappetence of unknown cause lasting less than one week. No owner requested withdrawal from the study due to concern of possible adverse drug effects.

Discussion

This is the largest case series to-date to describe cats with HST and DM treated with cabergoline. Although a direct measurement of insulin sensitivity was not performed, the trend for increasing requirement for exogenous insulin with similar serum fructosamine concentrations infers the cats experienced increasing insulin resistance. This is likely due to ongoing uncontrolled HST because cabergoline did not reliably control IGF1 concentration by decreasing it to within the reference interval.

There are no published studies describing the pharmacokinetics of cabergoline in cats. The plasma elimination half-life is between 63 to 109 hours in humans.[8] The initial dose of 5 µg/kg q24h by mouth was chosen because this was the licensed dose for the treatment of inappropriate lactation in cats, and this dose was effective in terminating pregnancy in queens which suggests effective suppression of prolactin secretion.[19] This dose is equivalent to 0.5 mg q24h dose for an average

222 human using mg/kg dosing, which is reported to result in GH suppression in
223 humans with acromegaly.[20] However, other studies have reported using higher
224 doses of cabergoline to treat cats and the medication was well tolerated, and some
225 humans with acromegaly require higher doses to achieve biochemical response.[21,22]
226 This was part of the rationale for increasing the initial cabergoline dose from 5 to
227 10 µg/kg q24h for cats 4 to 9.
228
229 The findings of this study differ from the results of a case series of three cats with
230 HST and DM treated with 10 µg/kg q48h cabergoline for three months.[23] All the
231 cats in that study experienced decreased IGF1 and improved insulin sensitivity after
232 treatment. It is possible that the cause of HST in cats was different to the cause of
233 HST in this study as different pituitary adenoma subtypes are known to respond
234 differently to medical management.[24,25] Response to cabergoline therapy can also
235 vary depending on prior treatments, alternative splicing of DRD2 mRNA,
236 magnitude of dopamine receptor expression at the protein level or defective
237 signalling pathways downstream of DR2 stimulation. [26–29] It has been reported that

cats with hypersomatotropism have a moderate negative correlation between *DRD2* expression and pituitary size[7]. That data suggests that pituitary size might be related to cabergoline responsiveness, but there was no difference of pituitary size between those who experienced an IGF1 decrease versus those who did not in this study. The low number of patients enrolled on this study will be a limiting factor to identify the effect of pituitary size and cabergoline responsiveness. A study investigating the effect of DR2 protein expression and cabergoline responsiveness is indicated to better determine the variability of cabergoline effect between patients.

Cabergoline is typically recommended for the treatment of acromegaly in humans who have mild clinical signs and IGF1 concentrations less than 1.5 to 2 times above the reference interval.[5,30] There were 6/9 cats who had serum IGF1 concentrations > 2000 ng/mL at the start of the study and only two cats had IGF1 concentrations less than twice the laboratory reference interval. It is possible that the severity of HST in these cats was inappropriate for cabergoline treatment. Apart from decreasing

IGF1, cabergoline might exert antidiabetic effects by increasing insulin sensitivity without affecting GH levels.[31] This mechanism could explain the response of cat 5 who was receiving a lower dose of insulin and had lower serum fructosamine despite slightly increased IGF1 at day 90 compared to day 1.

Consideration and measurement of QoL is increasingly important when undertaking clinical studies and particularly important in veterinary medicine as a common reason for euthanasia of a cat with DM is owner perceived poor pet QoL.[32–34] Acromegaly is associated with reduced QoL in humans and improves but does not normalize with disease control.[35–38] Diabetes in cats is associated with owner perceived reduced QoL of their cat and improved DM control has been associated with improved QoL.[18,39] Quality of life scores did not improve during the study which could be explained due to poor biochemical control of either HST or DM.

Clinical signs that might have been compatible with drug-induced adverse effects include an episode of presumed acute pancreatitis in one cat, 2/9 cats experienced inappetence presumed not associated with pancreatitis and one cat, which had experienced inappetence, also experienced self-limiting small intestinal diarrhoea lasting less than one week. Gastrointestinal adverse effects of cabergoline have previously been reported in cats receiving 15 µg/kg q24h.[21] Nausea and vomiting and vertigo are the most commonly reported side effects in cabergoline treated humans with hyperprolactinaemia, affecting up to 1/3 of those treated.[40] Cabergoline does not appear to induce pancreatitis in humans, and it is possible the cat which experienced pancreatitis did so independent of cabergoline treatment. ~~Pancreatic pathology in cats with DM appears to be common. One study reported 83 % of diabetic cats having increased feline-specific pancreatic lipase activity (fPLI), which is a marker of pancreatic inflammation.[40] Post-mortem examinations of cats with DM describe up to half of patients having evidence of chronic pancreatitis and 5 % having evidence of acute pancreatitis at the time of~~

~~death.[41] Additional studies are required to determine if cabergoline treatment is associated with pancreatitis in cats.~~

In 2008, the Medicine and Healthcare products Regulatory Agency published a statement that cabergoline therapy might be associated with increased risk of cardiac fibrosis, and cardiac valvulopathy should be excluded prior to starting cabergoline therapy.[41] A recent systematic review concluded that the risk of cabergoline-associated valvulopathy in patients with prolactinoma is low, but the authors recommend an initial echocardiogram prior to starting cabergoline therapy.[42] Patient's affected by Parkinson's disease often receive cabergoline doses greater than 3 mg per day (around 40 µg/kg q24h for the average UK human) compared to 0.25 to 3 mg/week (equating to 3.125 to 39 µg/kg per week) in patients affected by prolactinoma and appear to have an increased risk of cabergoline induced cardiomyopathy.[43–45] The doses of cabergoline used in this study are more comparable with those used to treat prolactinoma than Parkinson's disease. Nonetheless, as 30 to 50 % of apparently healthy cats without a heart

murmur have echocardiographic evidence of heart disease, it is possible that the use of cabergoline might have contributed to progressive cardiac disease in patient 1 who died on day 82.[46,47] It is also possible this patient experienced progressive heart disease regardless of cabergoline therapy because HST in cats is associated with a hypertrophic cardiomyopathy phenotype and increased risk of congestive heart failure.[48] ~~As a result of the death of this patient, all subsequently enrolled patients underwent echocardiogram examination at enrolment and risk of progressive cardiac disease was discussed with owners. Owners were instructed to intermittently monitor their cat's resting respiratory rate at home because this is reported to be a sensitive indicator of congestive heart failure in cats.[16] Owners were instructed to contact the investigator if their cat's average resting respiratory rate was greater than 36 breaths per minute. No owner declined to enrol on the study after receiving this information and no further increased resting respiratory rate events occurred during the study period.~~

The low patient number will have affected the power of the study. However, this was a pilot study and as a previous report described a good response of three cats with diabetes and hypersomatotropism treated with cabergoline, this study provides evidence that not all cats experience a good response.[23] Another limitation is that IGF1 concentrations greater than 2000 ng/mL were not diluted to obtain the exact IGF1 concentration. The lack of exact IGF1 enumeration will have limited our ability to determine a difference during the study. ~~We wished to assess whether good control, as defined as IGF1 concentration within the reference interval, would be achieved~~. Nonetheless, despite this limitation we can be confident reporting that no cat achieved normalization of serum IGF1.

Conclusion

Although the study was underpowered, cabergoline does not appear to reliably control HST as the cats in this study did not achieve IGF1 control nor improved diabetic control.

Author note: Preliminary data from the study was presented as an oral research communication at 27th ECVIM CA Congress 2018.

Conflict of interest: none

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Ethical Approval: This work involved the use of non-experimental animals (owned or unowned) and procedures that differed from established internationally recognised high standards ('best practice') of veterinary clinical care for the individual patient. The study therefore had ethical approval from an established committee as stated in the manuscript.

Informed consent: Informed consent (either verbal or written) was obtained from the owner or legal custodian of all animals described in this work (nonexperimental animals) for the procedures undertaken (prospective studies). No animals or

humans are identifiable within this publication, and therefore additional informed consent for publication was not required.

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Figures

Figure 1. Patient serum IGF1 at time points day 1, 30 and 90. There was no significant change of insulin-like growth factor 1 during the study ($X^2(2) = 0.667$, $P = 0.805$).

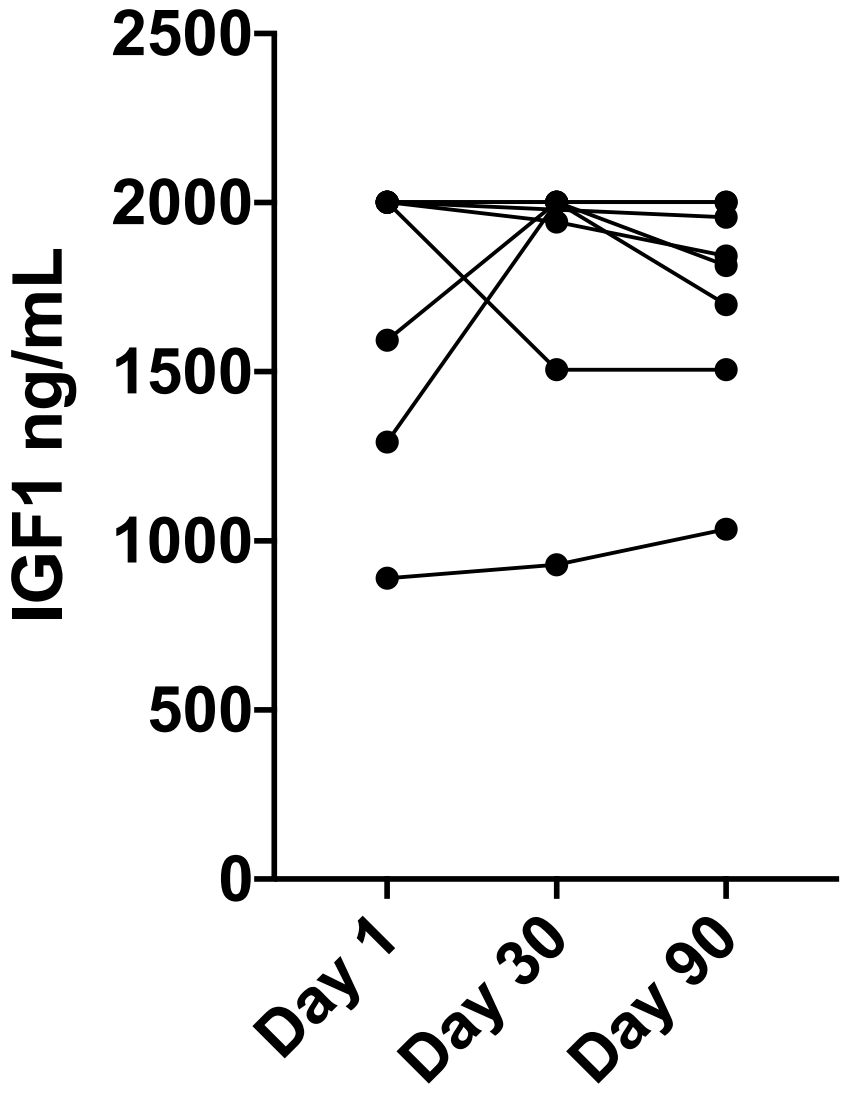

Figure 2. Patient serum fructosamine at time points day 1, 30 and 90. There was no significant change of fructosamine during the study, $X^2(2) = 0.581$, $P = 0.764$).

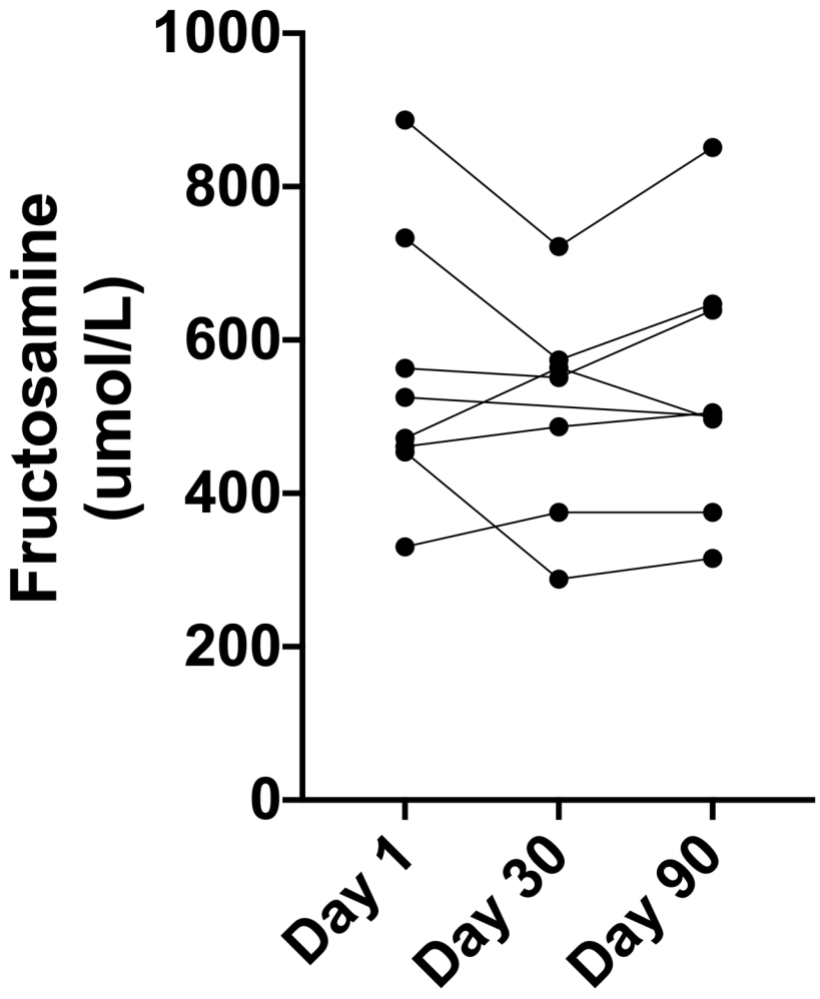

Figure 3. Patient insulin dose at time points day 1, 30 and 90. There was a significant change of insulin dose prescribed during the study ($X^2(2) = 8.667$, P = 0.008), with cats receiving higher insulin doses on day 90 compared to day 1 (median day 1 was 0.98 [range 0.63 to 1.49] and median day 90 was 1.56 [range 0.49 to 2.55] units/kg q12h, P = 0.026.)

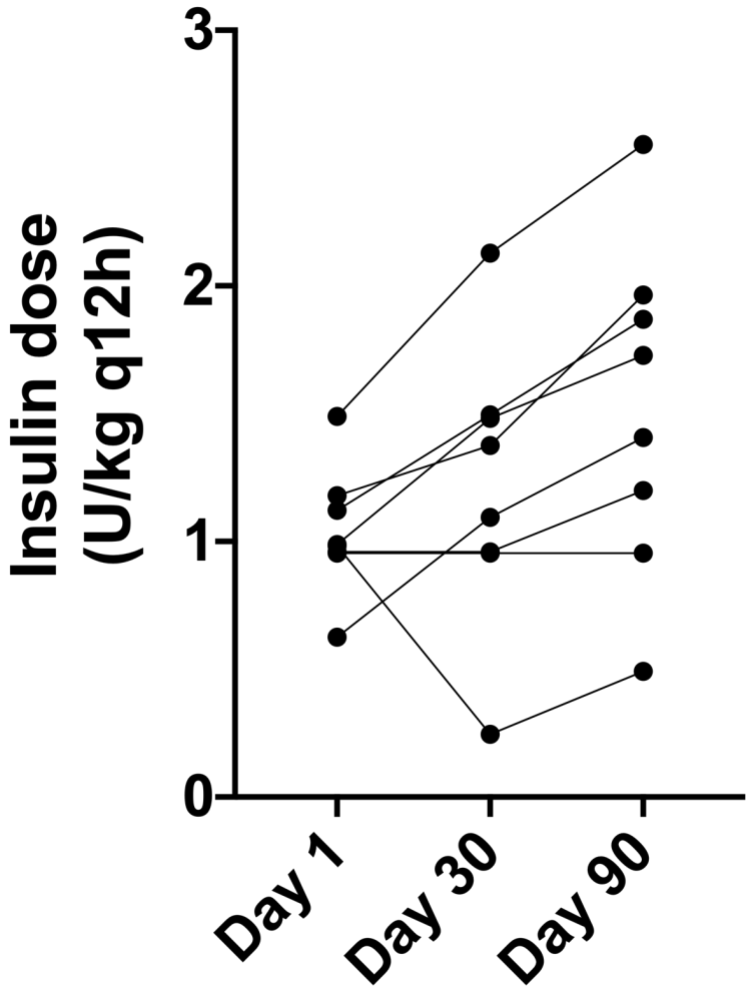

Figure 4. Patient DIAQoL-pet scores on days 1 and 90. There was no significant change of DIAQol-pet score (P = 0.715).