

EVALUATION OF THE FREESTYLE LIBRE 3 CONTINUOUS GLUCOSE MONITORING SYSTEM IN DIABETIC CATS

- INTRODUCTION AND SCIENTIFIC BACKGROUND

Insulin treatment requires close monitoring in cats with diabetes mellitus (DM). When dysglycemia is effectively controlled, cats are more likely to achieve diabetic remission as glucotoxicity is minimized. Traditionally, serial BGCs were the most recommended method for guiding insulin dose adjustments in diabetic cats. However, BGCs have several disadvantages, such as the need for repeated blood sampling and the risk of missing the blood glucose (BG) peak, nadir and trends over consecutive days. Moreover, repeated handling or restraining of cats can artifactually elevate BG concentrations, as cats are particularly sensitive to stress-induced hyperglycaemia.

In the last decade, the continuous glucose monitoring systems (CGMS) have revolutionized the management of diabetes mellitus (DM) in both human and veterinary medicine. These devices measure interstitial glucose concentrations (IG) on a minute-by-minute basis for up to 14 days, reducing blood sampling-associated patient discomfort and greatly increasing information on glucose fluctuations and trends. The FreeStyle Libre (Abbott Laboratories) is currently the most studied CGMS in veterinary patients. The accuracy of the first (FSL1) and the second generation (FSL2) of the FreeStyle Libre has been previously evaluated in healthy and diabetic cats. Despite the good clinical accuracy, the premature detachment of the sensor represents one of the most frequent complications in diabetic cats, with a median time of sensor activity ranging from 5 to 10 days. In 2020, a third generation of the device, FreeStyle Libre 3 (FSL3), has been licensed for use in diabetic people. The FSL3 measure IG using the same sensing technology as the FSL2. Like FSL2, the FSL3 provides continuous IG readings every minute, as well as offering glucose levels, trends, and alerts. However, the FSL3 has a new one-piece sensor applicator, and the sensor is about 70% smaller than FSL1 or FSL2. In a recent study, The FSL3 demonstrated accurate performance across the dynamic glycemic range in diabetic people. The smaller size of the FSL3 could be advantageous in veterinary patients, especially in cats, and clinical trials are warranted. The objective of this study is to evaluate the analytical and clinical accuracy of FSL3 in diabetic cats.

- **DESCRIPTION OF THE RESEARCH PLAN**

- Prospective and single-centre study
- Duration 12 months
- Inclusion criteria:
 - Client owned cats with diagnosis of DM on insulin treatment
 - Diagnosis of DM was performed according to the Agreeing Language In Veterinary Endocrinology (ALIVE) criteria established by the European Society of Veterinary Endocrinology (ESVE).
- Exclusion criteria:
 - Cats with dermatological abnormalities (e.g., hypercortisolism)
 - Aggressive cats
 - Outdoor cats

Freestyle Libre 3 CGMS: it is composed of a small-round sensor (21 mm × 2.9 mm). The sensor has a small catheter inserted under the skin, through which the sensor can measure the IG concentration. It can be worn for up to 14 days. The sensor will be applied as previously described. The detection limits of the sensor are between 40 and 500 mg/dL. The sensor begins recording data 1 hour after its application and automatically measures the IG concentrations every minute. The measurements are automatically recorded and stored on the sensor and displayed on the FreeStyle Libre 3 app. The data are automatically uploaded to LibreView when the phone is connected to the internet. This is a free, secure, cloud-based diabetes management system provided by Abbott. The system generates summary glucose reports from the uploaded sensor data, including the AGP and the Daily Log, and provides a secure repository for data.

- Study design:
 - The accuracy of the FSL3 will be assessed by comparison to a veterinary PBGM (AlphaTRAK®, Zoetis) previously validated for use in cats, used as a reference method. In order to compare IG obtained with FSL3 to the BG obtained with PBGM, paired samples will be collected. IG will be recorded using a smartphone connected to the FSL3 at the same time as each BG will be measured by the PBGM, and both

will be recorded as paired values. Paired measurements will be then classified in the hypoglycemic (<70 mg/dL), in the euglycemic range (70–180 mg/dL), and in the hyperglycemic range (>180 mg/dL). All the values above and below the detection limit of the sensor (≤ 20 and ≥ 500 mg/dL) will be excluded from the analysis.

- During the wearing period of the sensor, each cat will be evaluated for 3-time periods as follows: 1st day, 7th day, and 14th day. During every evaluation period, that lasts 12 hours, BG measurements will be recorded simultaneously every 1-2 hours.
- At the end of wearing period, all cats will be judged subjectively for the presence of erythema by the same clinician and the sensor lifespan will be recorded.

- **STATISTICAL ANALYSIS**

Statistical analysis will be performed with the aid of commercially available software. Normality will be assessed with the Shapiro–Wilk test and parametric or nonparametric tests will be used accordingly. Correlation between the IG measured by CGMS and BG measured by the PBGM will be evaluated with Spearman's rank correlation. The differences between IG and the BG will be plotted against the reference values in Bland–Altman plots. The Mann–Whitney test will be used to evaluate the interference by the presence of inflammation at the site of application.

Accuracy will be assessed according to ISO 15197:2013 guidelines, with acceptable analytical accuracy defined as 95% of IG results being within 15 mg/dL (when BG ≤ 100 mg/dL) or 15% (when BG >100 mg/dL) of paired BG, and clinical accuracy as $\geq 99\%$ of IG falling in zones A or B of the Parkes Error Grid analysis as formulated most strictly for people with Type I DM. Differences will be considered significant at $P < 0.05$.

- **EXPECTED RESULTS**

We speculate that FSL3 can be clinically accurate in diabetic cats. Furthermore, we hypothesize that the FSL3 will be better tolerated by cats, and the sensor's lifespan will be longer than that reported with previous generations of FreeStyle Libre. This could have a positive impact on the adherence and long-term use of CGMS in diabetic cats.

TIMELINE OF THE STUDY AND ROLE OF THE RESEARCH FELLOW

The study is going to last 12 months and it is going to be divided as follows:

- 9 months: recruitment of cats and collection of data.
- 3 months: data and statistical analysis, writing the abstract/article

The fellow will be involved in all operational phases of the research project starting with the selection and inclusion of cases. He/she will be primarily involved in data collection. He/she will then contribute to the processing and analysis of the results obtained with the aim of promoting scientific dissemination through oral communication at international conferences and articles published in peer-reviewed journals.

The fellow will also be involved in the clinical activity of the Veterinary Teaching Hospital of The University of Bologna (maximum 860 hours) and included in its continuing education, actively participating in weekly journal club meetings, book reading and interactive discussion of clinical cases.

Please note that in order to carry out this type of activity, the person concerned must have adequate insurance coverage. In particular:

- The contribution for membership in the University's professional insurance plan will be deducted from the first available payment.
- It is also advisable for the person concerned to verify their insurance coverage for gross negligence and activities carried out in the public sector.

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