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Short-term glycemic variability in non-diabetic, non-obese dogs assessed by common glycemic variability indices

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ABSTRACT

Glycemic variability (GV) refers to swings in blood glucose levels and is an emerging measure of glycemic control in clinical practice. It is associated with micro- and macrovascular complications and poor clinical outcomes in diabetic humans. Although an integral part of patient assessment in human patients, it is to a large extent neglected in insulin-treated diabetic dogs.

This prospective pilot study was performed to describe canine within-day GV in non-diabetic dogs with the aim to provide a basis for the interpretation of daily glucose profiles, and to promote GV as an accessible tool for future studies in veterinary medicine.

Interstitial glucose concentrations of ten non-diabetic, non-obese beagles were continuously measured over a 48-h period using a flash glucose monitoring system. GV was assessed using the common indices MAGE (mean amplitude of glycemic excursion), GVP (Glycemic variability percentage) and CV (coefficient of variation).

A total of 2260 sensor measurements were obtained, ranging from 3.7 mmol/L (67 mg/dL) to 8.5 mmol/L (153 mg/dL). Glucose profiles suggested a meal-dependent circadian rhythmicity with small but significant surges during the feeding periods. No differences in GV indices were observed between day and night periods ($p > 0.05$). The MAGE (mmol/L), GVP (%) and CV (%) were 0.86 ($\pm$ 0.19), 7.37 ($\pm$ 1.65), 6.72 ($\pm$ 0.89) on day one, and 0.83 ($\pm$ 0.18), 6.95 ($\pm$ 1.52), 6.72 ($\pm$ 1.53) on day two, respectively.

The results of this study suggest that GV is low in non-diabetic dogs and that glucose concentrations are kept within narrow ranges.

1. Introduction

Canine diabetes mellitus (CDM) is a life-threatening disease that usually requires lifelong therapy with major challenges for the patient, owner, and veterinary practitioner. The current treatment mainly aims to control clinical signs such as polyuria, polydipsia, polyphagia and weight loss whilst avoiding hypoglycemic events (Behrend et al., 2018; Feldman et al., 2015). A common recommendation is to target blood glucose concentrations below the renal threshold throughout most of the day while accepting a certain degree of variability (Behrend et al., 2018). Even though this approach usually leads to owner satisfaction, it disregards late sequelae including diabetic cataract and associated lens capsule rupture as well as uveitis, retinopathy, glomerulopathy, distal and autonomous neuropathy and cardiomyopathy (Braund and Steiss, 1982; Fein, 1990; Herring et al., 2014; Howell et al., 2013; Kenefick et al., 2007; Kern and Engerman, 1990; Pirintr et al., 2012; Struble et al., 1998; Vichit et al., 2018). A major argument for this conservative approach is that DM affects older dogs (Fall et al., 2007) with a short median survival time of 8–32 months (Cartwright et al., 2019; Fall et al., 2007; Tardo et al., 2019) and therefore most dogs supposedly do not live long enough to face long-term diabetic complications (DCs). This rationale, however, neglects the fact that a third of diabetic dogs are still alive three years after the initial diagnosis (Fall et al., 2007), a timespan which has previously been demonstrated to allow the development of diabetic complications (Beam et al., 1999; Kern and Engerman, 1990; Struble et al., 1998; Vichit et al., 2018).

In human medicine, even mild DCs are linked to a deteriorating quality of life and a significant reduction of life expectancy (Lloyd et al.,

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2001; Maddigan et al., 2005). Growing evidence suggests that not only chronic hyperglycemia, but also increased glycemic variability (GV), the amplitude, frequency, and duration of glucose fluctuations around the mean, is an independent risk factor for DCs (Nalysnyk et al., 2010; Tay et al., 2015). In vivo and in vitro studies suggest, that a high GV is more deleterious on endothelial function than consistently high glucose concentrations (Ceriello et al., 2008; Monnier et al., 2006; Risso et al., 2001). Other strong arguments for reducing GV include the association of within-day glucose fluctuations with cognitive impairment, emotional stress, increased risk for severe hypoglycemia and mortality in people (Eslami et al., 2011; Guelho et al., 2014; Kilpatrick et al., 2008; Kovatchev et al., 2003; Penckofer et al., 2012; Rizzo et al., 2010). Markers used to describe within-day GV are amongst others the standard deviation (SD), the coefficient of variation (CV), the mean amplitude of glycemic excursions (MAGE), the continuous overall net glycemic action (CONGA) and the glycemic variability percentage (GVP) (Peyser et al., 2018; Tay et al., 2015). Although some of these markers have already been used to describe GV in insulin-treated diabetic dogs (Fleeman and Rand, 2003; Miller et al., 2021; Ruaux et al., 2012; Zeugswetter and Sellner, 2020), studies assessing physiological within-day GV are scarce. This prospective study was initiated to describe the GV and diurnal glucose variations in non-diabetic dogs, using a flash glucose monitoring system (FGMS). The aim was to provide a preliminary basis on which glycemic control can be interpreted and to promote within-day GV, especially MAGE and GVP as accessible tools for future studies and diabetes monitoring in veterinary medicine.

2. Material and methods

2.1. Study population

Ten male, purpose-bred and neutered beagles from the University of Veterinary Medicine Vienna, Austria were enrolled in a prospective study from August to November 2020. The dogs are frequently used in the clinical education of students and as blood donors outside of the study period. All procedures performed on these dogs were approved by the Austrian ethical committee (ETK 072/04/2020). The mean ($\pm$ SD) age of dogs was 3.2 $\pm$ 1.2 years. The mean body weight was 15 kg $\pm$ 1.86, and the mean body condition score (BCS) was 5 $\pm$ 0.8 out of 9. The dogs were up to date on vaccinations (distemper, canine adenovirus 1, canine parvovirosis, canine kennel cough, rabies, leptospirosis) and regularly dewormed. At the time of enrolment into the study all dogs were attested healthy through clinical examination, dipstick urinalysis (Combur 9 Test, Roche Diagnostics, Switzerland, Basel), a complete blood count (ADVIA 2120i, Siemens Healthcare Diagnostic Products Ltd., Glyn Rhonwy, Llanberis, U.K.), biochemical (Cobas c501, Roche Diagnostics, Basel, Switzerland) and hormonal analysis (Immulite 2000, Siemens Healthcare Diagnostic Products Ltd., Glyn Rhonwy, Llanberis, U.K.). These included glucose, total protein, albumin, creatinine, alkaline phosphatase, alanine aminotransferase, sodium, potassium, total calcium, phosphate, lipase (DGGR-assay), fructosamine, cCRP, β-hydroxybutyrate, total T4 and canine TSH. All analyses were performed at the university's central laboratory within one week of sensor placement. Only dogs with fasting glucose concentrations <8 mmol/L (144 mg/dL), fructosamine concentrations <370 μmol/L and absence of glucosuria were considered. This is in line with the previously proposed definition of overt CDM (Gilor et al., 2016). Six months after the sensor-wearing period, the dogs were re-examined (clinical examination, dipstick, CBC, biochemical and hormonal analyses) to exclude unidentified diseases.

2.2. Sensor application and data collection

The factory-calibrated flash glucose monitoring system (FGMS, FreeStyle Libre, Abbot, Chicago, Illinois) consists of a sensor with a circular shape measuring 35 $\times$ 5 mm with a flexible 5 mm long filament located at the bottom center, a manufacturer-provided applicator, and the reading device or mobile phone application. The sensor is loaded onto the applicator, which is used to introduce the filament into the subcutaneous tissue via a cannula which is automatically retracted during the placement process. The FGMS was applied as previously described (Corradini et al., 2016, Zeugswetter and Sellner, 2020) in the following order. A dorsolateral area on the neck, approximately 10 $\times$ 10 cm in size, located halfway between the cranial border of the scapula and the caudal border of the auricle, was clipped and cleaned using a commercial skin disinfectant (Cutasept®F, BODE Chemie GmbH, Hamburg, Germany). After the disinfectant had evaporated, the sensor was applied and secured in place.

After a calibration phase of one hour, the sensor automatically records the interstitial glucose concentration every 15 min. The detection limit of the sensor is 2.2 to 27.8 mmol/L (40 to 500 mg/dL) and readings outside of these limits are given as "low" or "high".

The study consisted of a preliminary phase lasting from the time of sensor application between 9 and 11 a.m. (day 0) until 6 p.m. of the same day, followed by a 48-h study phase consisting of two full 24-h glucose profiles (profile 1 and 2). Profile 1 and 2 were further divided to obtain two 12-h night (night 1 and 2; 6 p.m.–6 a.m.) and two 12-h day profiles (day 1 and 2; 6 a.m.–6 p.m.) including up to 48 interstitial glucose measurements (4 per hour x 12), respectively.

During the study period, the dogs were housed in separate 1x1x1.5 m kennels, within sight of one another. The kennel room featured a clear glass door through which the dogs could perceive natural light intervals and additional electronic light was provided between 6 a.m. and 9 p.m. not using a specific timetable. Since the study was conducted between August and November natural light intervals were variable. The dogs were fed their regular dry diet (Gastrointestinal, Royal Canin, Mars Incorporated, Aimagures, France) twice daily between 7:30 and 8:30 a. m. and p.m., respectively, and had unlimited access to fresh water. In addition to three to four short walks lasting five to ten minutes during the day-time, they were taken on extended walks lasting at least one hour twice daily between 9 a.m. and 11 a.m. and 5 p.m. and 7 p.m. Glucose measurements were transmitted from the sensor to the handheld reader at least four times daily to avoid data loss. Data were uploaded to the online application LibreView (Abbot, Chicago, Illinois) provided by the manufacturer. In case of premature sensor detachment, a new sensor was applied and a new preliminary phase was initiated. In case of early sensor detachment data from the interrupted 24-h recording period was discarded. This study thus includes two continuous 24-h profiles of each of the ten dogs. Completed 24-h periods were stored and considered during analysis. Proper sensor function was verified every 8 h (6 measurements/dog) by comparing interstitial measurements with blood glucose concentrations using a hexokinase reference method (Catalyst One Chemistry Analyzer, Idexx, Maine, USA) (reference range 4.28–8.33 mmol/L (77–150 mg/dL)). For each measurement, one mL of blood was obtained via routine jugular venipuncture using a 20 gauge cannula attached to a 2 mL syringe and stored in a lithium heparin tube. Whole blood samples were spun at 4000 rpm and analyzed by the chemistry analyzer within 10 min of acquiring the blood samples.

2.3. Statistical analysis

All statistical analyses were performed using IBM SPSS version 27, IBM Corporation, Armonk, NY). Differences between days (day 1 vs day 2) and phases (night vs day) in mean glucose, GVP and MAGE were analyzed using linear mixed-effects models where day and phase were added as fixed factors to the models. Post hoc comparisons between factor levels were performed using Sidak's alpha correction procedure. The assumption of normal distribution was checked using the Kolmogorov-Smirnov test. Values are presented as mean ($\pm$ SD). The correlation between serum and interstitial glucose concentrations was assessed using Spearman's rank correlation coefficient. For all statistical analyses, a p-value <0.05 was considered significant. To identify and better visualize daily rhythmicity, glucose measurements obtained within every hour ($n = 4$) were consolidated, and changes were depicted as percent deviations from the individual mean daily glucose concentrations (Fig. 1). To investigate within-day GV, CV (SD divided by mean), MAGE (Service, 2013), and GVP (Peyser et al., 2018) were determined. The MAGE was calculated by hand using the method introduced by Service (Service, 2013) which is displayed in Fig. 2. where the sum of all glycemic excursions of more than one SD is divided by the total number of excursions added. The GVP is the total length of the glucose profile tracing (L) relative to the shortest possible tracing (L_0) which is a horizontal line equal to the time under investigation (GVP = (L/L_0−1) x 100). The difference in glucose concentrations (Δglucose) and the time elapsed between two consecutive time points (t) are used to calculate the length of a section of the glucose tracing (l) using the Pythagorean theorem $\sqrt{\Delta glucose^2 + t^2} = l$. The sum of all sections is the total length of line L (Peyser et al., 2018). All measurements displayed glucose concentrations in mg/dL.

2.4. Animal study approval

The protocol and procedures employed were ethically reviewed and approved by the Austrian Ministry of Education, Science, and Research.

3. Results

3.1. Clinical and laboratory examinations

During the study period, apart from mild epiphora (3/10), and sporadic coughing (5/10), no other signs of disease were observed. All dogs completed the full study period. Although 6/10 dogs initially had a borderline low T4 concentration, all but one dog had a normal T4 at the follow-up examination. All dogs had normal TSH concentrations and none developed clinical signs or biochemical changes suggestive of hypothyroidism within the 6-month follow-up period.

3.2. Sensor application

Sensor application was considered painless in all dogs. The sensor was generally well tolerated, but excessive scratching at the application site caused premature sensor detachment in three dogs. Mild to moderate erythema at the application site was observed in 4/10 dogs, but no intervention was necessary.

3.3. Sensor data

The entire recording period included a total of 2260 sensor measurements. The number of measurements and mean (± SD) for every specific recording period is shown in Table 1. Twelve (0.53%) measurements showed glucose concentrations <4.4 mmol/L (<80 mg/dL) and 1 (0.04%) showed a glucose concentration > 8 mmol/L (>144 mg/dL). The lowest measurement was 3.7 mmol/L (67 mg/dL) and the highest 8.5 mmol/L (153 mg/dL). The latter was observed during the preliminary phase. Simultaneous glucose concentrations measured with the reference method at 8-h intervals to test proper sensor function (58 pairs, two pairs missing) were in mean − 1.96% ± 10.4% (range: −16.8% to 24%) lower than the sensor measurements. As glucose concentrations did not reach a steady state until after midnight of night 1 (night after the preliminary period), the measurements from night 1 were excluded from statistical analyses. For results see Table 1, Figs. 3, and 4.

Interstitial glucose concentrations were significantly higher at eight and 9 a.m. of day 1 ($p = 0.01$; $p < 0.01$) and seven and 10 p.m. of night 2 ($p = 0.04$, $p = 0.02$) and significantly lower at 2 p.m. of day 1 (p = 0.01), four and 5 a.m. of night 2 (p < 0.01, p < 0.01) and one and 2 p.m. (p < 0.01, p < 0.01) of day 2.

Differences between day 1 and day 2 measurements, as well as between day 2 and night 2 were not significant for CV (day 1–2, $p = 0.99$; day 2-night 2, $p = 0.66$), MAGE (day 1–2, $p = 0.54$; day 2-night 2, $p = 0.97$), or GVP (day 1–2, $p = 0.55$; day 2-night 2, $p = 0.21$).

4. Discussion

The results of this pilot study using a flash glucose monitoring system suggest that GV is very low in healthy, adult and non-obese dogs and

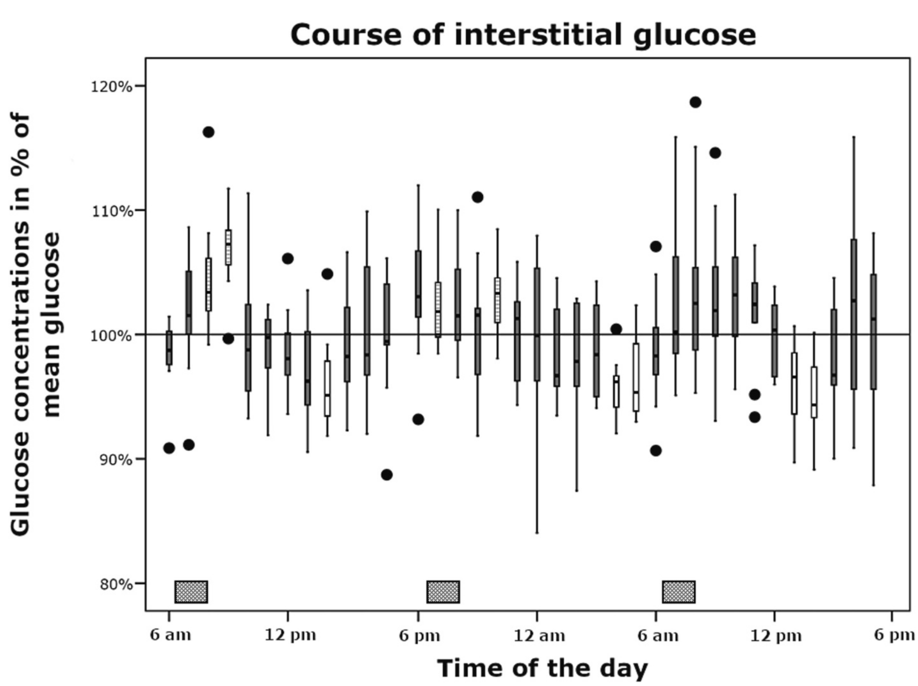

Fig. 1. Course of interstitial glucose throughout the 36-h study period.

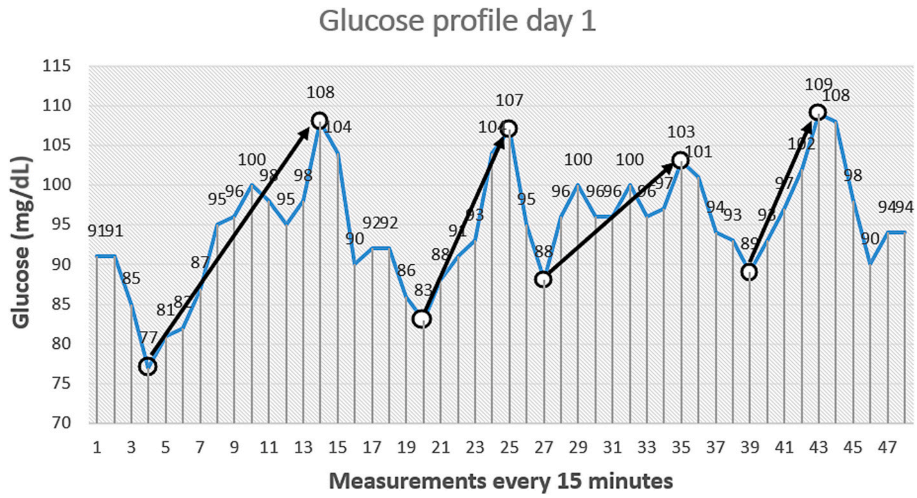

Fig. 2. Calculation of the mean amplitude of glycemic excursion (MAGE).

Table 1
Descriptive overview of sensor data and glycemic variability indices for each test segment. Night and day segments represent 12-h periods with nights starting at 6 p.m. Glycemic variability indices were not calculated for the preliminary phase and night 1 as glucose did not reach a steady state in these segments. Mean glucose and mean amplitude of glycemic excursion (MAGE) are given in mg/dL and mmol/L while the coefficient of variation (CV) and the glycemic variability percentage (GVP) are given in %. Data is displayed as mean (± SD).

		Preliminary phase	Night 1	Day 1	Night 2	Day 2
Measurements	number	355	478	477	478	472
Mean glucose	mg/dL	118.41 (± 4.84)	106.7 (± 5.45)	99.18 (± 8.64)	98.1 (± 11.16)	98.31 (± 9.72)
	mmol/L	6.57 (± 0.27)	5.92 (± 0.30)	5.51 (± 0.48)	5.45 (± 0.62)	5.46 (± 0.54)
MAGE	mg/dL	n.c.	n.c.	15.48 (± 3.48)	14.99 (± 3.52)	14.96 (± 3.27)
	mmol/L	n.c.	n.c.	0.86 (± 0.19)	0.83 (± 0.2)	0.83 (± 0.18)
CV	%	n.c.	n.c.	6.72 (± 0.89)	6.44 (± 1.26)	6.72 (± 1.53)
GVP	%	n.c.	n.c.	7.37 (± 1.65)	5.8 (± 2.35)	6.95 (± 1.52)

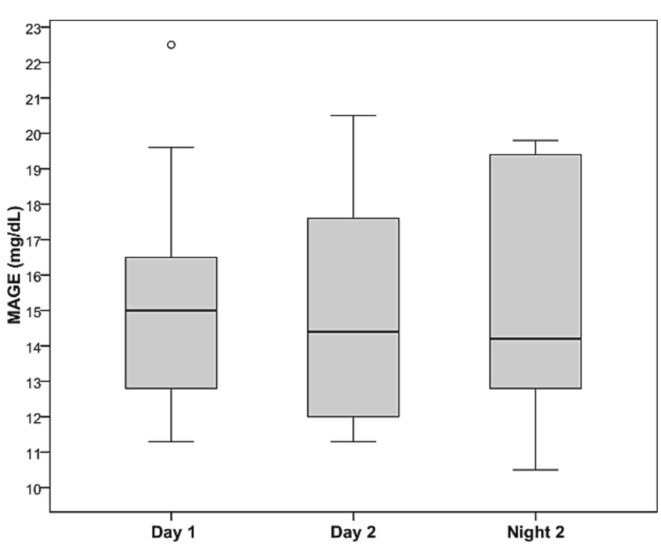

Fig. 3. Mean amplitude of glycemic excursion (MAGE) in 10 dogs.

that glucose concentrations are kept within narrow ranges. Although circadian rhythmicity was evident, the fluctuations hardly exceeded 10% of the mean daily glucose concentration. In line with an earlier study evaluating healthy dogs on a twice-daily feeding protocol (Fischer et al., 1985), significant glucose surges in the morning and evening were closely meal-related and the nadir was observed in the early afternoon. Notably, the effect of many types of insulin currently used in canine diabetology peaks at about 6 to 8 h after administration (Fleeman et al., 2009; Fracassi et al., 2012, 2015), a time that coincides with physiological low glucose concentrations. It is therefore not surprising that hypoglycemia is common during this "vulnerable" period (Zeugswetter and Sellner, 2020). A potential strategy for mitigating postprandial hyperglycemia and preventing low glucose concentrations in the early afternoon is to reduce the size of the morning meal and provide additional feeding at midday. Studies are needed to investigate whether this adapted feeding strategy significantly reduces GV in diabetic dogs.

Glucose concentrations <4.4 mmol/L (<80 mg/dL) only made up 0.53% of all measurements, which supports current treatment guidelines for diabetic dogs to aim for glucose concentrations above this limit (Behrend et al., 2018). Nevertheless, the presence of isolated measurements as low as 3.7 mmol/L (67 mg/dL), indicates that sporadic low glucose concentrations can be normal and that an insulin dose reduction by 25% (Rucinsky et al., 2010) or 10 to 50% (Behrend et al., 2018) may not be imperative in every case.

The average MAGE in the present study was 0.86 mmol/L (15.5 mg/dL) on day 1 and 0.83 (14.3 mg/dL) on day 2 and thus clearly lower than the previously reported numbers in non-obese, non-diabetic human adults (MAGE 1.46 mmol/L (26.3 mg/dL) to 1.57 mmol/L (28.3 mg/dL)), (Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, 2010; Ma et al., 2011) or in normoglycemic morbidly obese people (MAGE 2.7 ± 1.4 mmol/L (48 ± 26 mg/dL)) (Salkind et al., 2014). The highest MAGE in our study population was 1.3 mmol/L (22.5 mg/dL). The MAGE was initially introduced into diabetology as the "gold standard"for the assessment of short-term

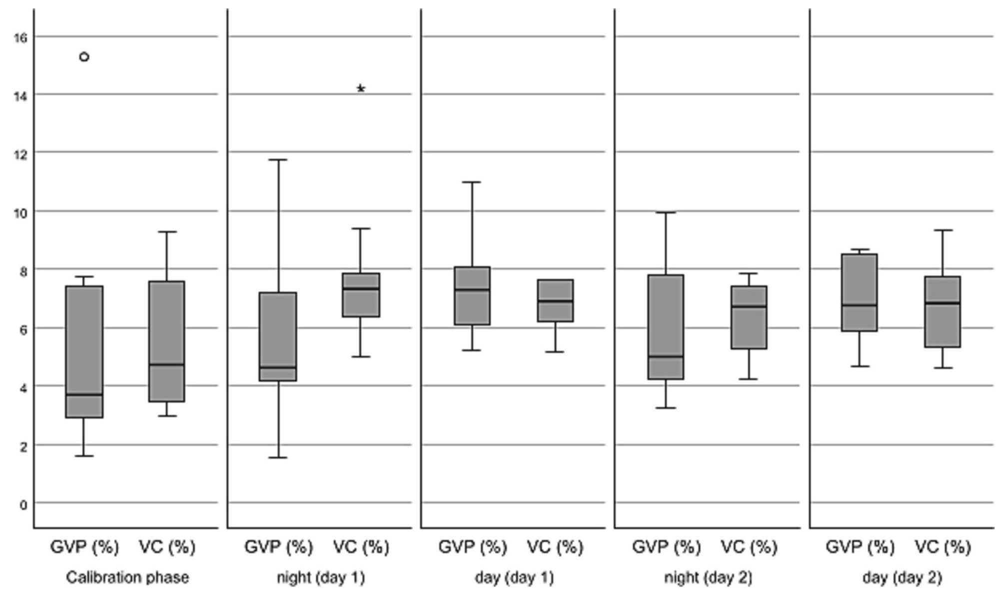

Fig. 4. Glycemic variability percentage (GVP) and coefficient of variation in 10 dogs,

variability in 1970 (Service, F.J, et al., 1970). Its purpose lies in assessing the mean amplitude of glycemic swings and its calculation spares sophisticated mathematical formulas. To avoid the incorporation of minor deviations, only glycemic excursions (peak to trough or trough to peak) exceeding one SD of the glucose measurements from the investigated time period are considered. The first ascending or descending excursion >1 SD is used as a starting point and added to all subsequent excursions. The arithmetic mean of these excursions represents the MAGE and a high MAGE represents increased within-day GV (Suh and Kim, 2015). The latter has been associated with various micro- and macrovascular complications including coronary artery disease, diabetic peripheral neuropathy, nocturnal hypoglycemia and mortality in diabetic people (Zhou et al., 2020). In a recent study, the MAGE was introduced as a measure to quantify GV in 24 insulin-treated diabetic dogs and revealed excessively high values of 13.2 ± 5.8 mmol/L (237 ± 105 mg/dL) even though some owners considered that the disease was well-controlled in these dogs (Zeugswetter and Sellner, 2020). Similar MAGE values are observed in humans with uncontrolled or fulminant DM (Ratna et al., 2017; Ying et al., 2019). In contrast, a population of individuals with Type-2 diabetes following a stable treatment regimen showed an average MAGE (± SD) of 6.48 ± 2.7 mmol/L (116.8 ± 48.8 mg/dL) in a recent study (Shivaprasad et al., 2021).

Another new metric recently introduced into canine diabetology is the glycemic variability percentage (GVP) (Miller et al., 2021). It provides a quantitative measurement of GV over a given time and in contrast to SD, CV or MAGE captures not only the amplitude but also the frequency of glucose fluctuations (Peyser et al., 2018). In contrast to the MAGE small high-frequency fluctuations also contribute to this parameter (Rodbard, 2018). The total length of the glucose profile's temporal trace is calculated by summation of the trace length between every consecutive measurement from the continuous glucose monitoring dataset by using trigonometric analysis, specifically the Pythagorean theorem. The sides of the Pythagorean triangle are represented by the glucose concentration difference and the time between two consecutive measurements and the length of the trace between them is analogous to the length of the hypothenuse. The total line length is then put in relation to the length of the shortest possible line in the corresponding time interval, visualized as a straight horizontal line and expressed as a percentage. The final calculation was performed using the mathematical formula provided by Peyser et al. The GVP is a time-independent measure as it is normalized to the duration of time under investigation (hours, days, weeks, months). A high GVP represents high variability. It is important to consider that the numerical values depend on the unit of time and glucose concentrations (mg/dL or mmol/L) used when performing the calculations (Rodbard, 2018). The mean GVP in our healthy beagles was 7.37 ± 1.65% on day 1 and 6.95 ± 1.52% on day 2. A recent study compared the effects of three different types of insulin on the GVP in dogs with streptozotocin-alloxan-induced diabetes (Miller et al., 2021). Like in the current study, beagles were used and measurements were performed every 15 min using mg/dL units. With a twice daily insulin and feeding protocol as well as a strict treatment algorithm, the mean GVP for a lente insulin was 192 ± 45.1% and superior to the GVP of insulin glargine 300 U/mL (237 ± 20.6%) or insulin degludec (215 ± 36.3%). Studies are now needed to show whether high GV increases the risk of adverse outcomes in dogs with spontaneous diabetes mellitus. It is currently unknown which of these parameters is most appropriate to describe GV in dogs. Until more is learned in this regard we recommend a multimodal approach to studying GV in veterinary medicine.

When discussing the results of this study various limitations have to be considered. Only a small number of dogs was investigated and the research environment was strictly controlled. Although the exercise and feeding protocol might resemble the living conditions of pet dogs, the GV is likely higher under real-life conditions. It is also obvious to assume that concurrent diseases, environmental factors, as well as emotional stress might cause fluctuations and increase short-term GV in the general dog population. All dogs in this study were male, of the same breed, some even from the same pedigree and of similar age. Age and sex may influence GV in dogs. While age was associated with higher GV in people, no difference in SD or MAGE was found between men and women (Zhou et al., 2011).

In conclusion, this study suggests that GV represented by the MAGE and GVP is low in healthy adult non-obese dogs and that glucose concentrations are kept within narrow ranges. Although meal-dependent circadian rhythmicity was evident, the fluctuations were minor and rarely exceeded 10% of the mean daily glucose concentrations in individual dogs. The present study provides a preliminary foundation for interpreting glucose profiles in insulin-treated diabetic dogs and marks the initial step in advocating the use of the MAGE and GVP as two new measures to describe short-term GV in veterinary practice and research. The results of this study further support the hypotheses that diabetic dogs show extreme GV compared to healthy animals and that the discrepancy between non-diabetic and diabetic individuals is even more pronounced in dogs than in humans.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT [OpenAI] in order to improve readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

CRediT authorship contribution statement

Tobias Urbanschitz: Conceptualization, Data curation, Formal analysis, Investigation, Project administration, Resources, Visualization, Writing – original draft, Writing – review & editing. **Lukas Huber:** Data curation, Investigation, Writing – review & editing. **Alexander Tichy:** Conceptualization, Data curation, Formal analysis, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. **Iwan Anton Burgener:** Funding acquisition, Project administration, Resources, Writing – review & editing. **Florian Karl Zeugswetter:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

None.

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