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Short- and long-term effects of dapagliflozin as an adjunct to insulin therapy in diabetic dogs: A pilot study

Taís Bock Nogueira
Universidade Federal do Rio Grande do Sul
José Lucas Xavier Lopes
Universidade Federal do Rio Grande do Sul
Frederico Aécio Carvalho Soares
Denise Iparraguirre da Silva
Universidade Federal do Rio Grande do Sul
Caroline Bernardo Gusmão
Universidade Federal do Rio Grande do Sul
Gabriela Goulart Teixeira
Universidade Federal do Rio Grande do Sul
Álan Gomes Pöppl
gomespoppl@hotmail.com

Universidade Federal do Rio Grande do Sul

Short Report

Keywords: Sodium-glucose cotransporter 2, Oral hypoglycemic drug, Gliflozin, Canine

Posted Date: August 31st, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10767219/v1

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Additional Declarations: No competing interests reported.

Abstract

This study evaluated adjunctive dapagliflozin therapy in insulin-treated diabetic dogs to assess short- and long-term glycemic, clinical, and laboratory outcomes in dogs with naturally occurring diabetes mellitus. Six diabetic dogs received a compounded liquid oral dapagliflozin (CLODapa) formulation (0.088 ± 0.013 mg/kg once daily) in addition to ongoing insulin therapy for 100 days. We monitored continuous glucose monitoring (CGM) before and after treatment initiation, and serially assessed clinical, biochemical, and urinary parameters. Short-term dapagliflozin administration significantly reduced mean interstitial glucose, glucose nadir and peak values, and increased time within the target glucose range (60–250 mg/dL), while decreasing time above range. Glycemic variability increased, although no increase in time spent < 60 mg/dL or clinical hypoglycemia was observed; however, CLODapa's initial dosage was reduced in four dogs due to concerns about hypoglycemia, increased in one, and left unchanged in another. Long-term treatment was associated with reductions in fructosamine, systolic blood pressure, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and cholesterol concentrations. No evidence of diabetic ketoacidosis, urinary tract infection, electrolyte imbalance, or acid–base disturbance was detected. Unintentional weight loss was documented in three patients and required a ~ 25% increase in food intake. Adjunctive dapagliflozin showed promise in improving glycemic control in diabetic dogs while remaining well tolerated, supporting further investigation of SGLT2 inhibition in canine diabetology.

Introduction

Virtually all diabetic dogs are insulin-deficient at diagnosis (Behrend et al. 2018; Niessen et al. 2022) and require insulin therapy to control hyperglycemia, prevent diabetic ketoacidosis (DKA), and survive, resembling human type 1 diabetes mellitus (T1D) (Fleeman and Gilor 2023). Despite the use of modern insulin analogs (Tardo et al. 2024; Mott et al. 2025), continuous glucose monitoring (CGM) systems (Del Baldo et al. 2025), and commercial and home-made diabetic diets (Tardo et al. 2025), glycemic control in some diabetic dogs remains challenging (Behrend et al. 2018; Kuzi et al. 2023), as also observed in humans (Mazzota et al. 2024). Strategies to improve glycemic control in human T1D, such as adjunct SGLT2 inhibitor (SGLT2i) therapy, remain controversial because they increase DKA risk; however, potential benefits are recognized (Maran et al. 2025).

Adjunctive SGLT2i therapy has been explored in a few recent veterinary studies and may provide benefits (An et al. 2024, 2025; Box et al. 2024). Dapagliflozin as an add-on therapy (Dandona et al. 2018; Mazzota et al. 2024) was approved in some human T1D scenarios, and despite the description of its metabolic effects in a canine model of insulin resistance (Kabir et al. 2023) and some studies on the cardiovascular (Saengklub et al. 2025; Massey et al. 2026) and urinary (Pakhawala 2026; Umezawa et al. 2026) effects of this specific SGLT2i in dogs, its use in canine diabetes remains undocumented. Therefore, this pilot study aimed to characterize the short- and long-term impact of adding dapagliflozin to insulin therapy on CGM, laboratory, and clinical outcomes of naturally occurring diabetic dogs.

Material and methods

Animals

This non-controlled clinical trial included six insulin-treated dogs with diabetes mellitus (DM): five spayed females (three Poodles, one Pinscher, one Shih-Tzu) and one neutered male Yorkshire Terrier. Median DM duration was 7 months (range 2–29), and mean age was 9.83 ± 2.31 years. Owners signed an informed consent form prior to the dog´s inclusion. The Ethics Committee on Animal Use in Research (CEUA/UFRGS) approved the study (protocol 48053). Insulin regimens were Glargine 300U q12h in three dogs, Glargine 100U q12h in one dog, NPH q12h in one dog, and a basal-bolus regimen with Glargine 300U + NPH q12h in one dog.

Protocol

Dogs were evaluated at baseline (D0) and at 10 (D10), 40 (D40), and 100 (D100) days after dapagliflozin initiation. To enable dose titration, dapagliflozin was administered as a compounded liquid oral formulation (CLODapa) at 0.088 ± 0.013 mg/kg once daily, given at home by owners without changes to insulin therapy or feeding protocol.

Short-term evaluation assessed interstitial glucose (IG) metrics obtained with a CGM system (FreeStyle Libre 2, Abbott), previously validated in diabetic dogs (Del Baldo et al. 2025). The IG was monitored for a median of 5 days (range, 4–8) before initiating dapagliflozin and 13.5 days (11–20) after. Raw data were downloaded (.csv) from the manufacturer website (LibreView) to calculate mean IG, glycemic variability (GV%), and percentage of time (%T) < 60 mg/dL, within target range (60–250 mg/dL), and > 250 mg/dL.

Long-term evaluations at each time point included insulin dose, physical examination, body weight, Diabetes Clinical Score (DCS) (Niessen et al. 2022), and systolic blood pressure measured by vascular Doppler according to Acierno et al. (2018). Laboratory assessments comprised complete blood count (CBC), serum biochemistry (albumin, beta-hydroxybutyrate (BHB), fructosamine, glucose, creatinine, SDMA, ALP, ALT, AST, phosphorus, cholesterol, triglycerides, urea, electrolytes [Na+, K+, iCa2+, Cl–]), venous blood gas analysis (VBGA), and urinalysis, including urinary protein-to-creatinine ratio (UPC).

All blood samples were collected after a 12-hour fast. CBC parameters were determined on an automated analyzer (Procyte DX, IDEXX), followed by manual differential counting. Serum biochemistry and UPC were evaluated on an automated analyzer (CM200, Wiener Lab). BHB was determined using a point-of-care ketometer (FreeStyle Optium Neo, Abbott). Electrolytes and VBGA were performed in an automated analyzer (Cobas b121, Roche). The product of insulin dose every 12 hours by fructosamine (mmol/L) was considered to determine the insulin resistance index (Gostelow et al. 2017).

Statistical Analysis

Data distribution was assessed by the Shapiro-Wilk test. Paired t-tests or Wilcoxon signed-rank tests were used for pre- and post-CLODapa CGM comparisons according to parametric or non-parametric data distribution, respectively. Comparisons across time points were performed using repeated-measures ANOVA with Tukey's post hoc test or the Friedman test with Dunn's post hoc test, as appropriate. Analyses were conducted using GraphPad Prism 8.0.1.

Results

Short-term analysis showed reduced mean post-CLODapa IG ($P = 0.0006$, Fig. 1a), insulin resistance index ($P = 0.031$, Fig. 1b), nadir glucose ($P = 0.034$, Fig. 1c), and maximum glucose ($P = 0.029$, Fig. 1d), whereas GV% increased ($P = 0.0003$, Fig. 1e). Time < 60 mg/dL was unchanged ($P = 0.176$, Fig. 1f), while time within 60–250 mg/dL increased ($P = 0.03$, Fig. 1g) and time > 250 mg/dL decreased ($P = 0.03$, Fig. 1h).

Long-term evaluations showed reductions in ALT ($P = 0.02$), AST ($P = 0.001$), ALP ($P = 0.04$), total cholesterol ($P = 0.01$), fructosamine ($P = 0.04$), and systolic blood pressure ($P = 0.01$, Fig. 2a). No differences ($P > 0.05$) were observed in body weight (Fig. 2b), DCS (Fig. 2c), daily insulin dose (Fig. 2d), triglycerides, BHB, electrolytes, VBGA, proteinuria, or other evaluated variables (Table 1). No clinical hypoglycemia occurred, and no cataract progression was observed in the three patients without cataracts at enrollment. CLODapa dosage was reduced in four dogs due to concerns about low IG, increased in one, and remained unchanged in one (Fig. 2e). Three dogs experienced unintentional weight loss, managed with a ~ 25% increase in food intake.

Table 1

Selected parameters from the complete blood count, serum biochemistry, electrolytes, venous blood gas analysis, and urinalysis from six naturally occurring diabetic dogs on insulin therapy and monitored for 10 (T10), 40 (T40), and 100 (T100) days after initiating (T0) with dapagliflozin as an adjunctive therapy.

Hematocrit (%)	**T0**	**T10**	**T40**	**T100**
	47.8 ± 5.41	**46.5 ± 4.63**	**44 ± 2.94**	**45.7 ± 2.94**
Albumin (g/L)	33.2 ± 4.45	33.3 ± 3.61	32.5 ± 5.78	33.5 ± 4.03
ALP (U/L)	360.5 ± 172	**279.5 ± 124[a]**	**247.5 ± 103[a]**	**184.7 ± 39.1[a]**
ALT (U/L)	142.5 (49–269)	**93.5 (72–145)[b]**	**40 (12–106)[b]**	**54.5 (27–258)[b]**
AST (U/L)	40 ± 10.7	35 ± 9.52	**21.7 ± 10.7[c]**	34.8 ± 4.99
Creatinine (mg/dL)	0.6 ± 0.1	0.6 ± 0.21	0.58 ± 0.22	0.63 ± 0.18
Urea (mg/dL)	39.2 ± 10.38	44.33 ± 14.16	30.3 ± 9.71	40.7 ± 7.94
SDMA (µg/dL)	6.2 ± 2.23	7.2 ± 2.78	6.33 ± 0.81	6.5 ± 1.51
Phosphorus (mg/dL)	4.97 ± 1.11	4.88 ± 1.07	4.15 ± 0.93	4.7 ± 0.98
Glucose (mg/dL)	204.5 (57–537)	211.5 (48–325)	229.5 (49–346)	229.5 (172–345)
Fructosamine (mmol/L)	445.0 ± 120.3	**309.0 ± 69.61[d]**	**311.7 ± 97.48[d]**	**311.5 ± 97.2[d]**
Triglycerides (mg/dL)	133 (43–238)	179 (47–236)	76.5 (53–111)	118 (42–375)
Cholesterol (mg/dL)	294.8 ± 70.82	265.3 ± 85.22	**258 ± 56.13[e]**	268.3 ± 94.6
ß-OH-Butirate (mmol/L)	0.25 (0.1–0.3)	0.30 (0.2–1.2)	0.30 (0.2–1.2)	0.3 (0.3–0.7)
Na^{++} (mEq/L)	146.7 ± 4.47	146.6 ± 3.54	148.3 ± 4.69	146.2 ± 2.47
K^{+} (mEq/L)	4.24 ± 0.85	4.04 ± 0.39	4.06 ± 0.6	4.77 ± 0.38
Cl^{-} (mEq/L)	106.7 ± 3.84	108.7 ± 2.42	108.9 ± 2.65	106.6 ± 1.91

[a] Statistically different than T0 (0.0486)

[b] Statistically different than T0 (0.0256)

[c] Statistically different than T0 (0.0012)

[d] Statistically different than T0 (0.0454)

[e] Statistically different than T0 (0.019)

Hematocrit (%)	**T0**	**T10**	**T40**	**T100**
	47.8 ± 5.41	**46.5 ± 4.63**	**44 ± 2.94**	**45.7 ± 2.94**
iCa^{++} (mEq/L)	1.27 ± 0.08	1.29 ± 0.03	1.25 ± 0.08	1.26 ± 0.04
pH (venous)	7.36 ± 0.03	7.35 ± 0.02	7.37 ± 0.03	7.37 ± 0.03
HCO_3^- (mEq/L)	22.74 ± 2.04	22.46 ± 2.66	22.16 ± 2.89	22.96 ± 2.61
Sodium (mEq/L)	146.7 ± 4.47	146.6 ± 3.54	148.3 ± 4.69	146.2 ± 2.47
Specific urine gravity	1,038 ± 0,009	1,030 ± 0,015	1,038 ± 0,009	1,043 ± 0,006
Bacteriuria (+)	0 (0–2)	0.5 (0–2)	1 (0–2)	0 (0–2)
Ketonuria (+)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
Glucosuria (+)	3 (0–4)	3.5 (2–4)	4 (3–4)	4 (2–4)
Urine protein: creatinine	0.1 (0.04–0.29)	0.08 (0.03–0.32)	0.06 (0.01–0.18)	0.05 (0.01–0.17)
[a] Statistically different than T0 (0.0486)				
[b] Statistically different than T0 (0.0256)				
[c] Statistically different than T0 (0.0012)				
[d] Statistically different than T0 (0.0454)				
[e] Statistically different than T0 (0.019)				

Bold parameters showed significant variations in the long-term

Discussion

This study represents the first report of dapagliflozin combined with insulin therapy in dogs. The protocol improved short-term glycemic control by reducing mean CGM glucose, nadir, and maximum IG, while increasing time within range and decreasing time above range. The absence of clinical hypoglycemia, ketosis, and unchanged time < 60 mg/dL supports short-term safety with respect to DKA risk, although monitoring for low IG values, β-hydroxybutyrate, and weight loss remains necessary. Beyond inhibiting renal glucose reabsorption, dapagliflozin induces metabolic adaptations in dogs, including lipolysis, adipose tissue remodeling, and adipokine modulation (Kabir et al. 2023), as well as ketogenic and diuretic effects (Umezawa et al. 2026). Unintentional weight loss required progressive increases in food intake (meal size) in half of the patients to prevent clinically relevant loss. Insulin-sparing and weight-loss effects were reported after one year of monitoring diabetic dogs on long-term insulin therapy exposed to enavogliflozin as adjunctive therapy (An et al. 2024). In contrast, a multicenter study of

insulin-treated diabetic dogs on the same drug for eight weeks did not document weight loss (An et al. 2025), nor did another study evaluating short-term addition of canagliflozin to insulin therapy in diabetic dogs (Box et al. 2024).

The dapagliflozin dose previously reported in studies with non-diabetic dogs ranged from 0.3 to 1.25 mg/kg (Kabir et al. 2023, Saengklub et al. 2025; Massey et al. 2026), which were considered excessive for diabetic dogs on insulin therapy during the initial phase of this project, causing pronounced interstitial hypoglycemia and insulin-sparing effects. Yet, even with an initial dose of ~ 0.1 mg/kg in our study, most cases require reductions in the CLODapa dose. Consistent with our findings, Umezawa et al. (2026) described increased 24-hour urinary glucose excretion in healthy dogs treated with 1 and 0.3 mg/kg compared with dogs receiving 0.1 mg/kg. We did not specifically pursue insulin dose reduction; in fact, it can increase the risk of DKA and unintentional weight loss (Kabir et al., 2023; An et al. 2024; Maran et al. 2025). In fact, despite minor individual adjustments, the mean patient´s insulin dose during the study remained unchanged. We hypothesized that dapagliflozin would improve glycemic control, potentially limit chronic diabetic complications, and support translational relevance to human T1D, while also serving as an alternative to improve glycemic control in dogs with challenging glycemic control. Although IG decreased, GV% increased, likely reflecting early insulin and CLODapa dose adjustments and lower baseline pre-CLODapa GV% at higher glycemic ranges.

Adjunctive dapagliflozin showed promise for improving glycemic control in diabetic dogs and was associated with long-term reductions in systolic blood pressure, fructosamine, and liver enzymes. CLODapa was well tolerated, with no evidence of urinary tract infection or electrolyte or acid–base disturbances. Limitations of this pilot study include small sample size, canine diabetes mellitus heterogeneity, and variable insulin protocols; nevertheless, these findings support further investigation in this translational field and in veterinary practice.

Declarations

Ethical approval

The Animal Use Ethics Committee (CEUA) of the Universidade Federal do Rio Grande do Sul, Brazil, approved the study protocol (Project 48053), and all dog owners provided written informed consent.

Conflict of interest

All authors declare no conflict of interest.

Funding

This study was supported by the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES - Finance code 001),

and Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS – TO 25/2551-0002784-5), Brazil.

Author Contribution

T.B.N. and A.G.P conceptualizated, performed the formal analysis and investigation, and wrote the original draft. T.B.N., J.L.X.L., F.A>C.S., D.I.S., C.B.G. and G.G.T. were involved with methodology. A.G.P reviewed and edited the manuscript, and was responsible for supervision, visualization, and funding acquisition. T.B.N and J.L.X.L were responsible for resources. All authors reviewd the manuscript.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Figures

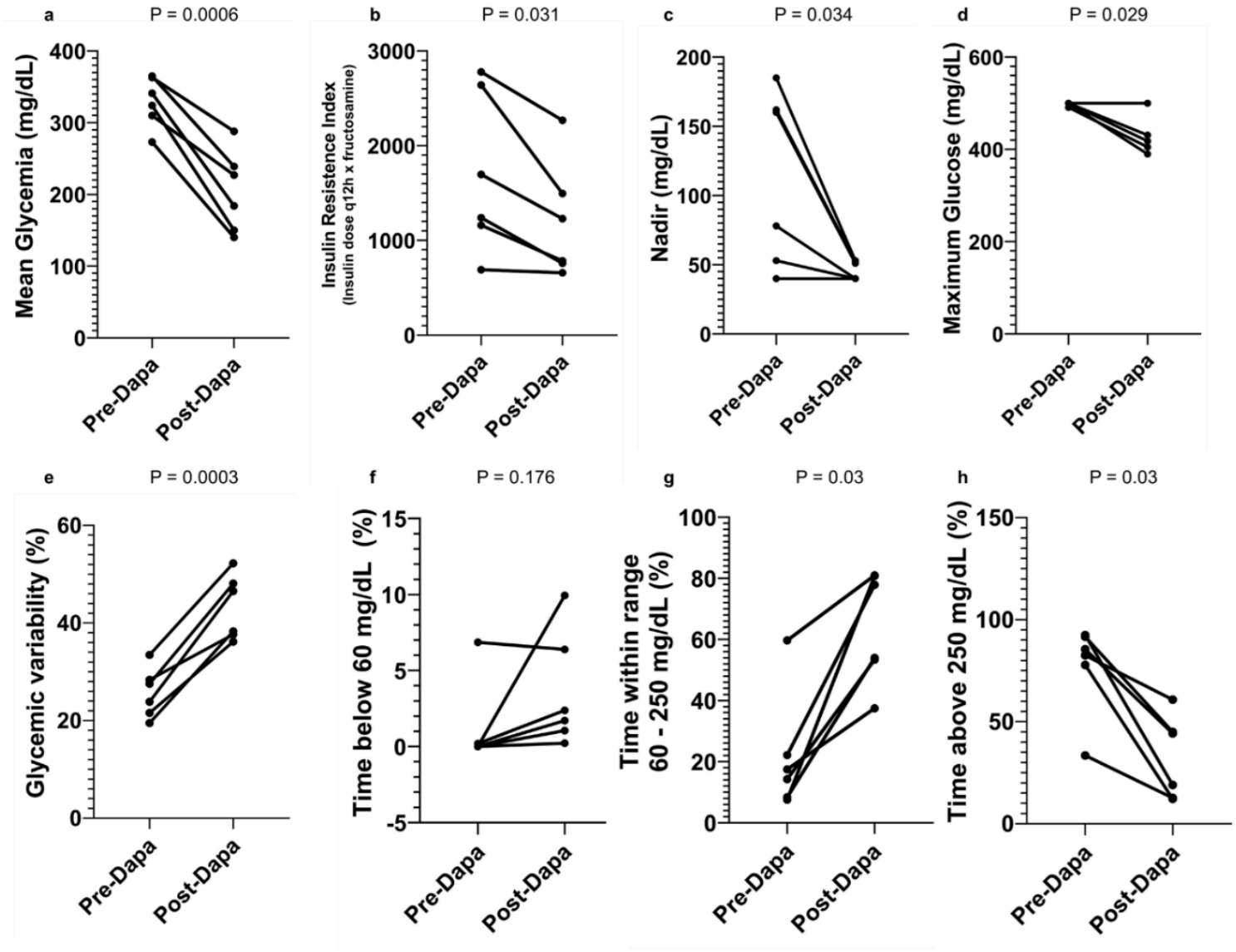


Figure 1

Short-term effects of dapagliflozin as an adjunctive therapy to insulin on continuous glucose monitoring (FreeStyle Libre 2) metrics in naturally occurring diabetic dogs. a. Mean interstitial glucose. b. Insulin resistance index (serum fructosamine x insulin dose q12h). c. Lowest documented interstitial glucose (nadir). d. Maximum documented interstitial glucose. e. Glycemic variability (%). f. Percentage of time with interstitial glucose below 60 mg/dL. g. Percentage of time with interstitial glucose between 60 and 250 mg/dL. h. Percentage of time with interstitial glucose above 250 mg/dL

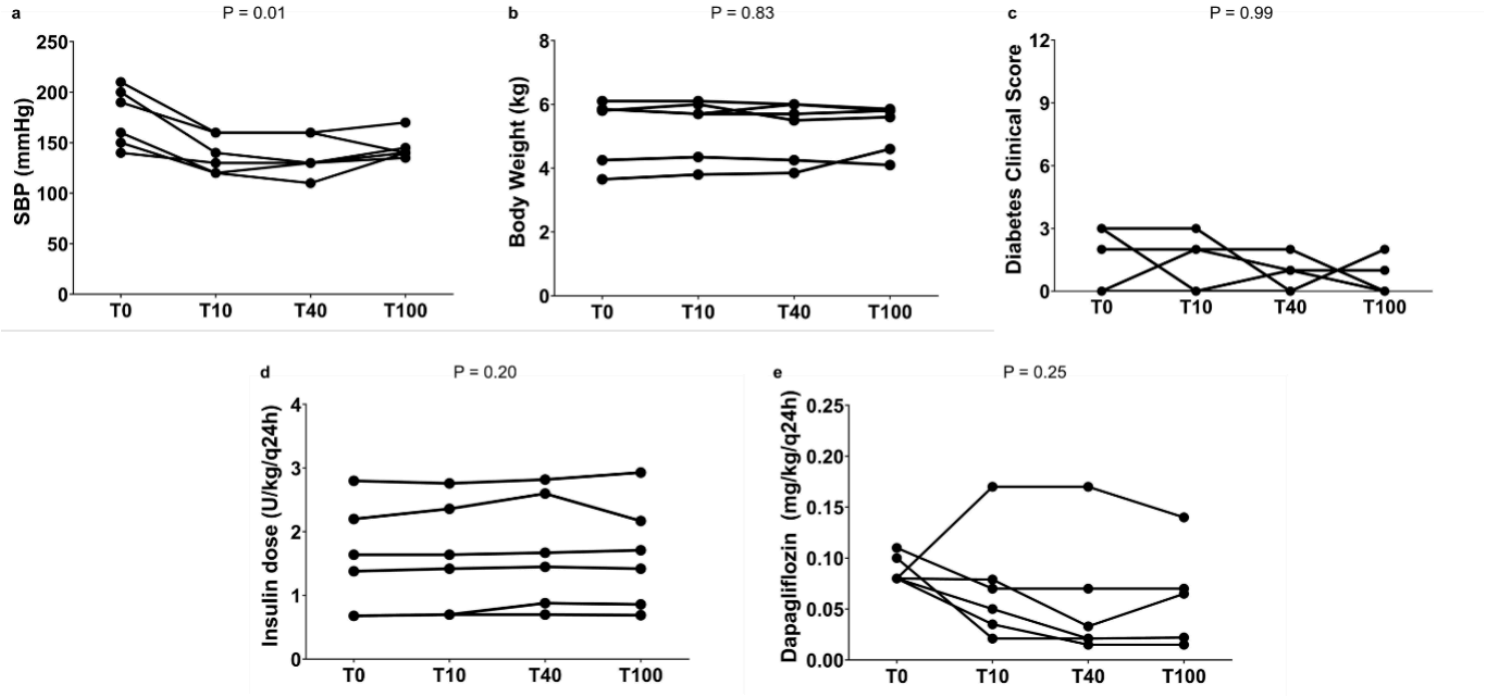


Figure 2

Long-term effects of dapagliflozin as an adjunctive therapy to insulin in naturally occurring diabetic dogs. a. systolic blood pressure (SBP) b. body weight c. Diabetes Clinical Score. Figures 2d and 2e depict the daily insulin dose and the daily dapagliflozin dose over the studied period, respectively