

Ciclosporin A therapy is associated with disturbances in glucose metabolism in dogs with atopic dermatitis

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Conflict of Interest

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Abstract

The effect of ciclosporin A (CsA) on glucose homeostasis was investigated in 16 dogs with atopic dermatitis by determining plasma glucose, serum fructosamine and insulin concentrations, and serial insulin and glucose concentrations following a glucagon stimulation test, before and 6 weeks after CsA therapy at 5 mg/kg once daily. All dogs completed the study. Following CsA treatment, the median serum fructosamine concentrations were significantly higher (pretreatment 227.5 $\mu\text{mol/L}$; post-treatment 246.5 $\mu\text{mol/L}$; $P = 0.001$; reference range 162–310 $\mu\text{mol/L}$). Based on analyses of the areas under concentration-time curves (AUC) pre- and post-CsA treatment, plasma glucose concentrations were significantly higher (AUC without baseline correction 31.0 mmol/L/min greater; $P = 0.021$) and serum insulin concentrations were significantly lower (AUC without baseline correction 217.1 $\mu\text{IU/mL/min}$ lower; $P = 0.044$) following CsA treatment. Peak glucose concentrations after glucagon stimulation test were significantly higher following CsA treatment (10.75 versus 12.05 mmol/L; $P = 0.021$), but there was no significant difference in peak serum insulin (52.0 versus 35.0 $\mu\text{IU/mL}$; $P = 0.052$). There was a negative correlation between baseline uncorrected insulin AUC and trough serum log CsA concentrations ($r = -0.70$, $P = 0.005$). The administration of CsA to dogs with atopic dermatitis leads to disturbances in glucose homeostasis. The clinical significance of this is unclear, but it should be taken into account when

considering CsA treatment in dogs that already have such impairments.

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Introduction

Ciclosporin A (CsA) is a calcineurin inhibitor that inhibits T-cell activation and prevents synthesis of several cytokines, notably interleukin-2 (IL-2).^{1,2} Without IL-2 stimulation, further T-cell proliferation is inhibited and T-cell cytotoxic activity is reduced. The marked ability to impair T-cell activation and proliferation has led to the use of CsA in a wide range of clinical scenarios in human and veterinary medicine.² Ciclosporin A shows variable efficacy in the treatment of many canine dermatoses, including atopic dermatitis (cAD),^{3,4} anal furunculosis,^{5,6} sebaceous adenitis,⁷ pemphigus foliaceus⁸ and sterile nodular panniculitis.⁹ A recent meta-analysis of 10 studies containing 799 dogs found that CsA was highly effective for the treatment of cAD and adverse effects were minimal.¹⁰ Ciclosporin A has also been used to treat a number of other canine conditions, including granulomatous meningoencephalitis¹¹ and myasthenia gravis.¹²

Early work indicated that CsA had a positive, protective effect on pancreatic β -cell function in experimental models of type 1, insulin-dependent diabetes mellitus.¹³ Ciclosporin A treatment was found to prevent the development of diabetes mellitus in nonobese diabetic mice, presumably by inhibiting T-cell activation, which prevented the T-cell-mediated destruction of insulin-producing pancreatic β -cells.¹³ Ciclosporin A has also been used in attempts to halt the progression of immune-mediated pancreatic islet cell destruction in people with recent-onset type 1 diabetes mellitus.¹⁴ Subsequent studies evaluating the effects of CsA administration in humans with or at risk of developing type 1 diabetes showed that CsA administration caused modest improvements in glycaemic control, albeit not as dramatically as in the nonobese diabetic mouse.^{15,16}

In contrast to the improvement in glycaemic control observed in experimental models of type 1 diabetes through modulation of autopathogenic, islet-reactive T cells, studies in transplantation medicine revealed that CsA can negatively disturb glycaemic control. For example, β -cell function was reported to be diminished in CsA-treated human recipients of pancreas and kidney allografts, and in dogs with autotransplants of segmental pancreatic tissue.^{17–19} A deterioration in glucose homeostasis has frequently been observed in human transplant recipients treated with CsA.¹⁷ The disturbance in glucose

homeostasis has been postulated to be caused either by increased tissue insulin resistance or by impaired insulin production and/or secretion.^{20–23} Ciclosporin A has been shown to inhibit insulin secretion in *in vitro* assays containing canine pancreatic islets²⁴ and *in vivo* assessment of islet pancreatic β -cell function in dogs.^{18,25,26} Despite the fact that overt diabetes mellitus has been only rarely described following CsA treatment in dogs,^{3,27–31} a study of pancreatic β -cell function³² revealed that after 3 weeks of CsA administration at 20 mg/kg, dogs remained normoglycaemic, but retrieved islet tissue showed a significantly lower total insulin output than that of control animals.³²

Nevertheless, the impact of microemulsified CsA on glucose homeostasis at standard licensed dosage rates for the treatment of canine dermatological conditions has been poorly studied to date. The primary aim of this study was to evaluate the impact of the licensed dosage of CsA on glucose metabolism in dogs with cAD. A secondary aim was to assess the efficacy of CsA therapy in order to confirm that the dosages used were clinically effective in the patients under investigation. Our hypothesis was that CsA in a microemulsion formulation administered at the recommended therapeutic dose once daily to atopic dogs would negatively impact glycaemic control. This hypothesis was tested by measuring fructosamine, glucose and insulin before and after CsA treatment at 5 mg/kg. In addition, the dogs had glucose and insulin serially measured following a glucagon stimulation test (GST) before and after CsA treatment.

Materials and methods

Study design

This study was undertaken in the Dermatology Unit of the Royal (Dick) School of Veterinary Studies [R(D)SVS], The University of Edinburgh between January 2009 and January 2010. Consecutive dogs with a clinical diagnosis of cAD according to well-established criteria³³ were considered eligible for the study. Diagnoses physically resembling cAD (e.g. ectoparasitic infestations or cutaneous adverse food reactions) were ruled out using standard diagnostic and therapeutic methods prior to inclusion in the study. Dogs with physical and laboratory evidence of secondary skin infections, e.g. bacterial pyoderma or *Malassezia* dermatitis, were treated to resolution prior to inclusion and, using topical therapy, as required if relapses occurred during the study. In addition, dogs that had received glucocorticoids in the previous 12 weeks were excluded. Following a standard therapeutic cascade, the atopic dogs were treated with CsA if the preparation of an allergen-specific immunotherapy vaccine was pending or immunotherapy had been discontinued due to lack of efficacy. No other treatments were allowed. A total of 16 consecutive atopic patients were selected to receive oral capsular CsA (Atopica[®]; Novartis Pharma AG, Basel, Switzerland) at as near as possible to the licensed dose of 5 mg/kg (range 4.4–6.0 mg/kg) once daily for 6 weeks.

After discussing the available data on the effects of glucose metabolism on canine pancreatic β -cell function, the owners of the dogs were offered the opportunity to have their pet's glucose metabolism closely monitored during CsA therapy. When owners consented, their dogs underwent a standard assessment of pancreatic β -cell function using an approach that has been widely validated in the dog.^{25,34,35} This included measurement of 12 h fasting plasma glucose, insulin, albumin and fructosamine concentrations prior to CsA administration and 6 weeks after treatment, together with trough (24 h after the last administration) serum CsA concentrations.³⁶ In addition, a GST was performed on dogs pretreatment and 6 weeks post-treatment.²⁵ The GST involved the injection through an intravenous catheter placed in a cephalic vein of 1 mg (dogs weighing more

than 10 kg) or 0.5 mg (dogs weighing 10 kg or less) of glucagon (GlucaGen HypoKit; Novo Nordisk Pharmaceuticals, Novo Allé, Bagsværd, Denmark). Fasting blood samples for insulin and glucose measurements were taken immediately before and 10, 20 and 30 min after glucagon administration. This gives an objective assessment of the ability of β -cells to secrete insulin pre- and post-treatment with CsA in response to a standardized secretagogue stimulus. When the glucose or insulin concentration following the GST is plotted on the y-axis and time along the x-axis, the area under the curve (AUC) provides an objective assessment of the overall response to the GST.

The venous blood samples for measurement of albumin, insulin and fructosamine concentrations were collected in plain tubes, and samples used for glucose determinations were harvested into fluoride oxalate-coated tubes.

Plasma glucose samples were centrifuged immediately and analysed in an on-site clinical pathology laboratory using a glucose hexokinase assay IL600 analyser (Instrumentation Laboratories Ltd, Warrington, UK). Pre-GST samples for analysis of serum albumin, insulin, fructosamine and CsA concentrations and post-GST samples for analysis of insulin were collected in plain glass tubes and allowed to clot at room temperature before centrifugation and harvesting of serum. Albumin was analysed on the day of blood sampling using a bromocresol green assay IL600 analyser (Instrumentation Laboratories Ltd). The remaining samples were stored at -80°C within 1 h of sampling.

Insulin was measured at Cambridge Specialist Laboratory Services (Stapleford, Cambridge) using an immuno-radiometric assay (INSI-CTK; Diasorin S.p.A., Saluggia, Italy). The inter- and intra-assay coefficients of variation were 2.6% and 4.8%, respectively. Fructosamine was measured by colorimetric assay and based on the ability of ketoamines to reduce nitroterazolum blue to formazan in an alkaline solution (Cobas Mira Plus analyser; Roche Diagnostics GmbH, Mannheim, Germany) with a measuring range from 10 to 1000 $\mu\text{mol/L}$. Intra-assay and interassay coefficients of variation were 1.0% and 2.9%, respectively.

Serum CsA concentrations were determined by tandem mass spectrometry. The sensitivity of the method was 25 $\mu\text{g/L}$, and the intra-assay coefficient of variation was between 4.8% and 7.1% over the 25–2000 $\mu\text{g/L}$ detection range.

The response to treatment was assessed by scoring the skin lesions of all dogs on days 0 and 42 using the canine atopic dermatitis extent and severity index (CADESI)-03 as previously described.³⁷ The owners used the Edinburgh Pruritus Scale to score the pruritus on a numerical scale (0–5) annotated with specific behavioural descriptors as previously described.³⁸

Investigations were performed in client-owned dogs with owner permission. The study was approved by The University of Edinburgh's Ethical Review Committee through the R(D)SVS's Veterinary Ethical Review Committee.

Statistical analyses

The effect of CsA treatment on differences between areas under concentration–time curves, peak glucose and insulin levels, and fructosamine and albumin concentrations was tested with Wilcoxon matched pairs tests. The confidence intervals for differences in median AUCs were estimated using bootstrap resampling. The correlation between glucose and insulin AUC and CsA concentration with and without baseline correction was evaluated by Pearson's product–moment correlation tests. The CsA data were log transformed to reduce skewing. Statistical significance was set at $P < 0.05$.

The result of the insulin assay from one dog was not available for the 20-min pretreatment measurement. An estimate was imputed as a median of the values assayed at 10 and 30 min. This approach was used for the corresponding post-treatment value for consistent analysis. Statistical analyses were performed with the R Statistical System.³⁹

Results

Sixteen dogs comprising 10 breeds were enrolled in the study (Table 1). Ten were male (nine castrated) and six

Table 1. Signalment and ciclosporin A (CsA) dose data of dogs enrolled in study

Dog	Breed	Sex	Age (years)	Weight (kg)	Daily CsA dose (mg/kg)
1	Boxer	MN	2.2	25.6	4.9
2	German shepherd dog	M	8.1	32.0	4.7
3	Labrador retriever	FN	4.6	22.8	4.4
4	West Highland white terrier	MN	3.9	8.4	6.0
5	Patterdale terrier	FN	2.0	10.0	5.0
6	Estrella mountain dog	MN	5.1	46.0	5.4
7	Fox terrier	MN	3.3	11.0	4.5
8	German shepherd dog	FN	4.2	32.5	4.6
9	Labrador retriever	FN	9.6	28.5	5.3
10	Golden retriever	MN	3.0	36.0	4.9
11	West Highland white terrier	MN	1.1	8.4	6.0
12	Rottweiler	MN	3.4	56.0	5.4
13	Miniature poodle	F	4.9	5.6	4.5
14	Labrador retriever	MN	2.7	40.0	5.0
15	West Highland white terrier	FN	1.2	9.4	5.3
16	Labrador retriever	MN	7.8	30.7	4.9

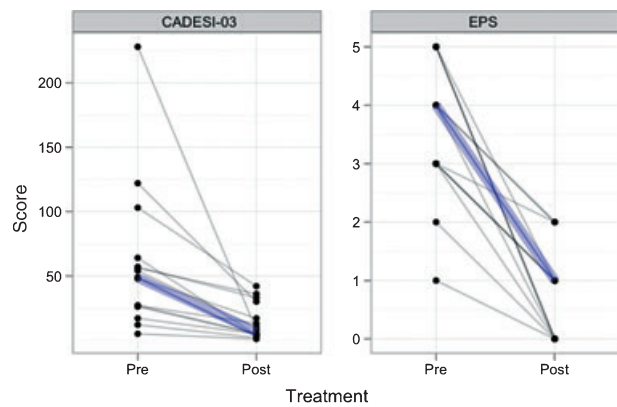
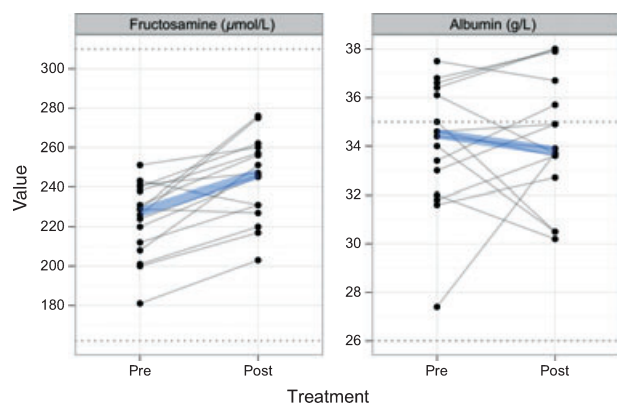
F, female; FN, ovariohysterectomized female; M, male; MN, castrated male.

were female (five ovariohysterectomized). Their ages ranged between 1.1 and 9.6 years (median 3.7 years) and they weighed between 5.6 and 56 kg (median 27.1 kg). All dogs completed the study. Mild adverse effects were seen in seven dogs following CsA therapy. These consisted of intermittent vomiting (two of 16; 12.5%) and soft stools (five of 16; 31%). In all affected dogs, the vomiting resolved within 7 days of beginning ciclosporin. The soft stools persisted while the five dogs were taking ciclosporin. One of the 16 dogs had an episode of diarrhoea within minutes of the glucagon injection. The signs disappeared without medical intervention.

Ciclosporin A treatment reduced CADESI-03 scores by $\geq 25\%$ in all 16 dogs and by $\geq 50\%$ in 14 of 16 dogs. Comparison of pruritus scores on days 0 and 42 indicated that treatment with CsA reduced pruritus by $\geq 25\%$ in 16 dogs and by $\geq 50\%$ in 15 of 16 dogs (Figure 1).

The median fructosamine concentration was significantly elevated after 6 weeks of CsA therapy (pretreatment median 227.5 $\mu\text{mol/L}$; post-treatment median 246.5 $\mu\text{mol/L}$; $P = 0.001$; reference range 162–310 $\mu\text{mol/L}$). Albumin concentrations were not significantly different pre- and post-treatment ($P = 0.717$; Figure 2).

The results of the glucose and insulin assays following the GST are presented by time point (Figure 3a) and by patient (Figure 3b,c). These graphs show that although there is some variation between dogs, overall the glucose concentrations were higher at 20 and 30 min post-GST following CsA treatment compared with pre-treatment. The glucose AUC with baseline correction was 27.0 mmol/min greater post-CsA treatment compared with pre-CsA treatment ($P = 0.017$; Table 2). Without correction for baseline value, the glucose AUC was 31.0 mmol/L/min higher post-treatment ($P = 0.021$; Table 2). The insulin AUC with baseline correction was 291.5 $\mu\text{IU/mL/min}$ lower post-treatment ($P = 0.062$) and without correction, the insulin AUC post-GST was

**Figure 1.** Canine atopic dermatitis extent and severity index-03 (CADESI-03) and Edinburgh Pruritus Scale (EPS) scores pre- and 6 weeks post-treatment with ciclosporin A (CsA). The shaded grey line in each figure connects the median values pre- and post-treatment.**Figure 2.** Serum concentrations of fructosamine and albumin concentrations pre- and 6 weeks post-CsA. The areas between the dotted grey lines represent the respective reference ranges. The shaded grey line in each panel connects the median values pre- and 6 weeks post-treatment.

217.1 $\mu\text{IU/min/mL}$ lower post-treatment ($P = 0.044$; Table 2).

Peak serum glucose concentrations post-GST were significantly higher post-treatment with CsA (pretreatment median 10.75 mmol/L; post-treatment median 12.05 mmol/L; $P = 0.021$). Peak serum insulin concentration post-GST was lower post-CsA treatment, but the difference was not statistically significant (pretreatment median 52.0 $\mu\text{IU/mL}$; post-treatment median 35.0 $\mu\text{IU/mL}$; $P = 0.052$).

Trough serum CsA concentrations were measured 24 h after medication in all 16 dogs, but detectable concentrations were present in only 14 samples. The median serum CsA concentration in the 14 samples was 21.25 $\mu\text{g/L}$ (range 0.2–1076 $\mu\text{g/L}$). In these 14 cases, the correlation between $\log[\text{CsA}]$ and baseline-uncorrected glucose AUC difference was 0.56 ($P = 0.036$), and that between $\log[\text{CsA}]$ and baseline-uncorrected insulin AUC difference was -0.70 ($P = 0.005$). The correlation between $\log[\text{CsA}]$ and baseline-corrected glucose AUC difference was 0.37 ($P = 0.19$) and between $\log[\text{CsA}]$ and baseline-corrected insulin AUC difference was -0.73 ($P = 0.003$; Figure 4).

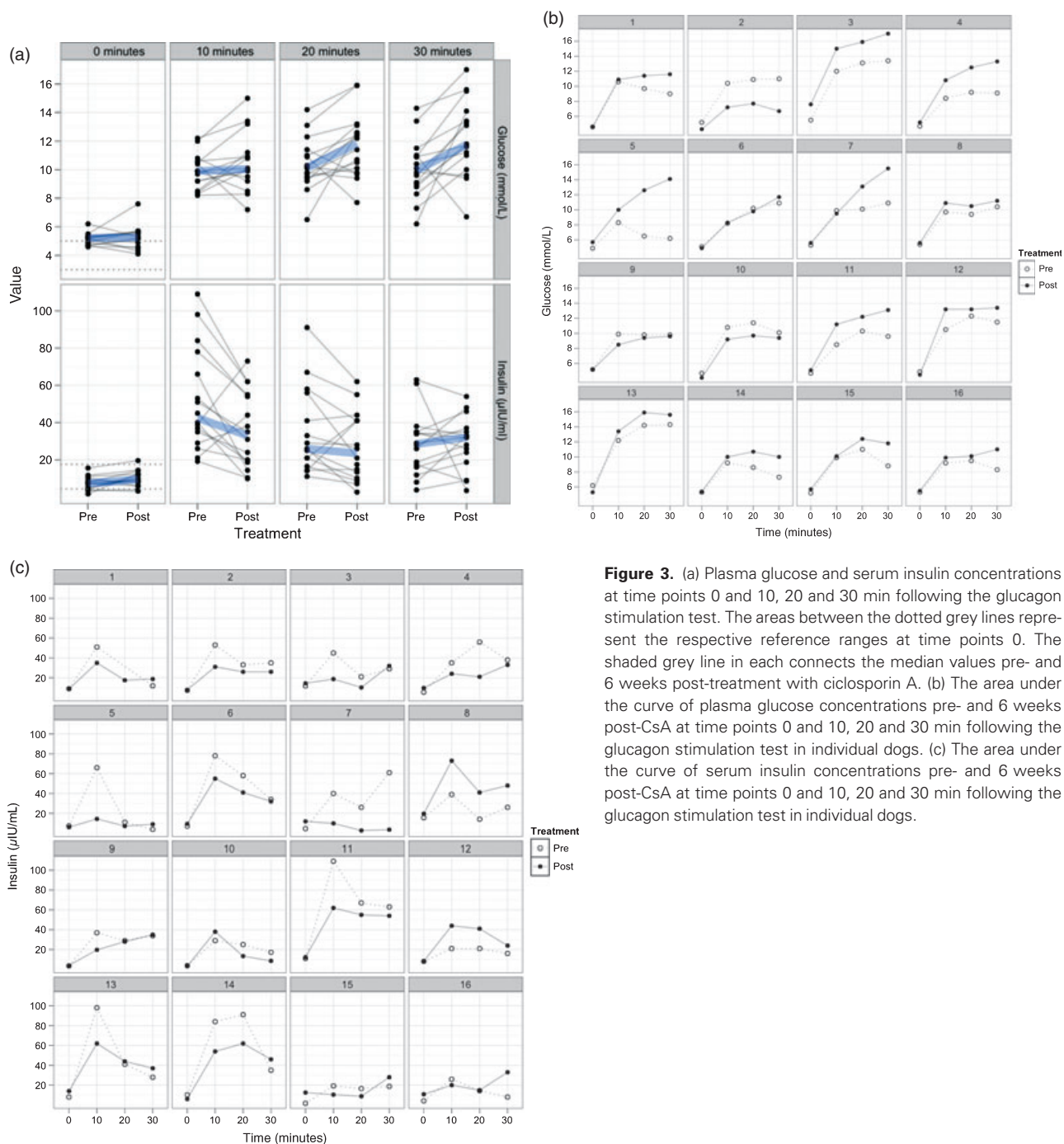


Figure 3. (a) Plasma glucose and serum insulin concentrations at time points 0 and 10, 20 and 30 min following the glucagon stimulation test. The areas between the dotted grey lines represent the respective reference ranges at time points 0. The shaded grey line in each connects the median values pre- and 6 weeks post-treatment with ciclosporin A. (b) The area under the curve of plasma glucose concentrations pre- and 6 weeks post-CsA at time points 0 and 10, 20 and 30 min following the glucagon stimulation test in individual dogs. (c) The area under the curve of serum insulin concentrations pre- and 6 weeks post-CsA at time points 0 and 10, 20 and 30 min following the glucagon stimulation test in individual dogs.

Discussion

The key finding of this study is that the licensed micro-emulsion formulation of CsA used successfully to manage cAD at the recommended 5 mg/kg dose once daily significantly disturbed glucose homeostasis. The measurement of fructosamine concentrations is frequently undertaken in cases of suspected diabetes mellitus, since the majority of diabetic dogs have a fructosamine concentration above the reference range.^{40,41} Albumin was concurrently measured because diseases which disturb serum protein concentrations can also alter fructosamine concentrations.⁴¹ The significantly increased serum fructosamine concentrations post-CsA treatment in the absence of significant alterations in albumin concentra-

tions clearly indicate that CsA therapy can negatively disturb glucose homeostasis, although the detected post-treatment disturbances were relatively mild because no dogs had a fructosamine concentration post-treatment above the reference range. The negative effect of CsA on glycaemic control is further emphasized by the finding that glucose concentrations 20 and 30 min after a GST, which is a dynamic stimulation test widely used to assess pancreatic β -cell function in dogs,^{25,34,35} were increased following CsA treatment, as was the overall glucose AUC post-CsA therapy.

This study did not clearly delineate the mechanism by which glycaemic control was negatively disturbed in this group of dogs. Indeed, it is also important to acknowledge that a control group of atopic dogs that were suc-

Table 2. Summary of insulin and glucose area under concentration–time curve (AUC) changes post-ciclosporin A treatment

Parameter	Difference between AUC post- and pretreatment (95% confidence interval)
Insulin ($\mu\text{U/mL/min}$)	
Without baseline correction	–217.0 (–392.9, –13.1)
With baseline correction	–291.5 (–471.6, –95.4)
Glucose (mmol/L/min)	
Without baseline correction	31.0 (5.88, 54.38)
With baseline correction	27.0 (8.44, 44.72)

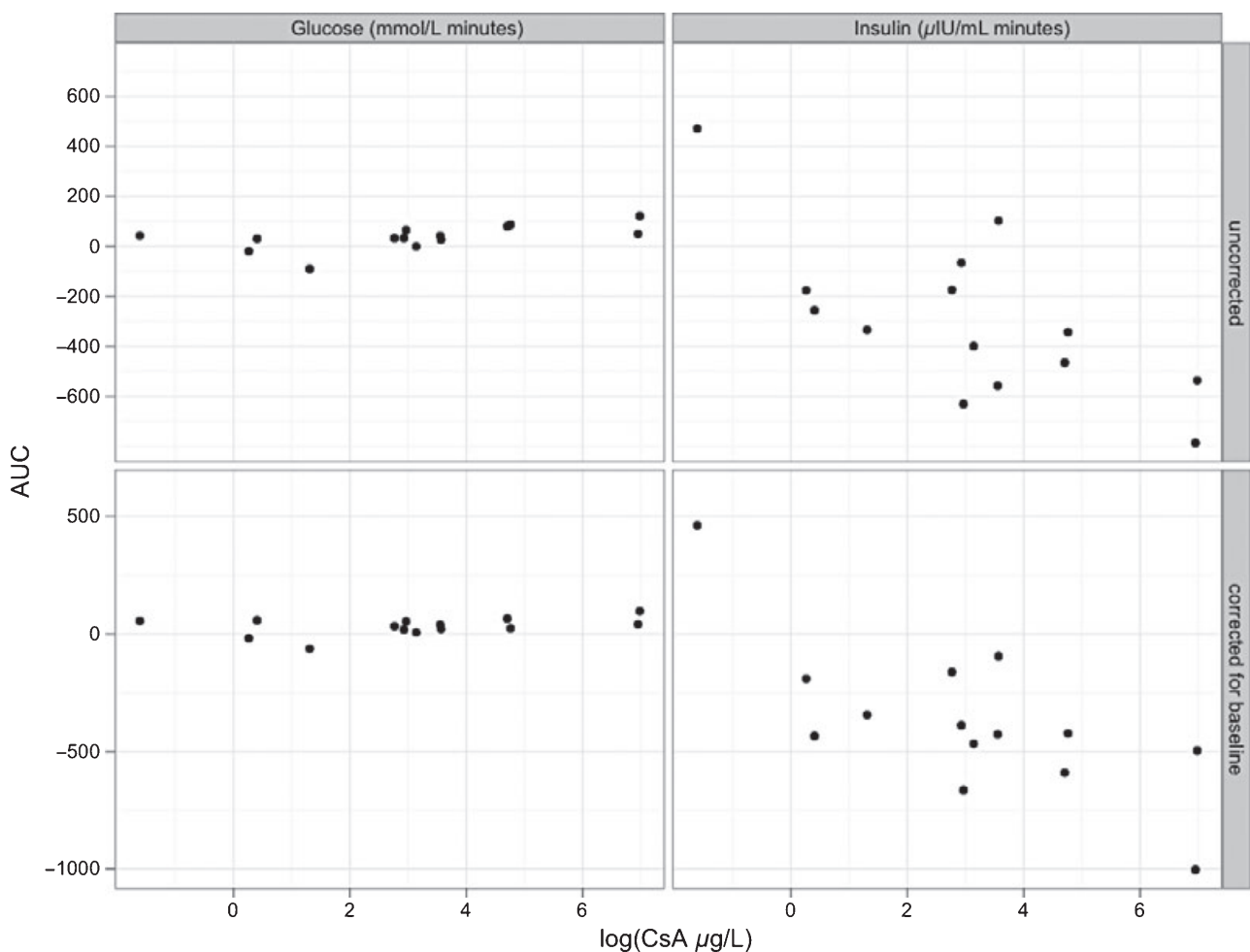
The AUC without baseline correction was calculated by measuring the area under the curve when the glucose or insulin concentrations were plotted on the y-axis and time along the x-axis. The AUC with baseline correction was calculated in the same manner, but in this case all the glucose and insulin concentrations had the initial baseline value subtracted.

cessfully managed by an alternative treatment, such as immunotherapy, was not included in this study, so it cannot be concluded definitively that CsA was the cause of the dysregulation in glucose homeostasis. However, the study did show that basal serum insulin concentrations were higher, and insulin secretion to a standard stimulus was reduced, post-CsA treatment as evaluated

by insulin AUC following GST. In addition, there was a negative correlation between insulin AUC following a GST and serum CsA concentrations. The reduced ability of islets to secrete insulin in response to a secretagogue stimulus offers a highly plausible explanation for the observed alterations in glucose homeostasis.

These findings are consistent with previous *in vitro* and *in vivo* studies of pancreatic β -cell function in dogs following CsA treatment.^{18,25,26,32,42,43} For example, a study of plasma glucose and insulin responses to intravenous glucagon in six healthy beagles before, during, and 1 and 4 months after the administration of CsA at a dosage of 20 mg/kg daily²⁵ reported that insulin secretion in response to glucagon was inhibited during the administration of CsA. This is consistent with our results using a lower licensed dosage of the microemulsion formulation. Similar results were also recorded in another study of the effects of CsA on glucose homeostasis, which reported increased insulin resistance following 10 weeks of 20 mg/kg daily of CsA,²⁶ and that the glucose AUC was significantly increased and insulin AUC significantly decreased post-CsA treatment following a GST. Wahlstrom *et al.*²⁶ also found that 20 mg/kg CsA administered to dogs decreased insulin release following a GST.

In support of these *in vivo* findings of CsA disturbance to glucose homeostasis in dogs, *in vitro* studies have also

**Figure 4.** Trough log serum ciclosporin concentrations uncorrected and corrected for baseline area under the concentration–time curve (AUC) post-glucagon stimulation testing for plasma glucose and serum insulin concentrations following ciclosporin A treatment.

found that CsA disturbs canine islet function. For example, Basadona *et al.* reported that after 3 weeks of CsA treatment at a dosage of 20 mg/kg/day, islets retrieved from CsA-treated animals had a significantly reduced insulin output.³² In addition, canine islets that were pre-treated for 24 h with CsA had reduced glucose-stimulated insulin secretion in a dose-dependent manner.²⁴

Studies on the effects of CsA on glucose homeostasis in other species have also found that CsA negatively disturbs glycaemic control. Studies of tacrolimus, another calcineurin inhibitor, and CsA in humans have shown that both are associated with impaired glucose metabolism and with post-transplantation diabetes mellitus.⁴⁴ Menegazzo *et al.*⁴⁵ treated male Wistar albino rats with 10 mg/kg/day of CsA. After 4 weeks of CsA administration, glucose intolerance due to decreased insulin production and impaired insulin action by a postbinding mechanism was demonstrated. In pigs treated with 100–140 mg/kg/day of CsA, insulin secretion was shown to be significantly decreased following a GST, whereas blood glucose concentrations were significantly increased.⁴⁶

The mechanism by which CsA disturbs glucose homeostasis remains unclear because studies have found both a direct effect on islet cell insulin content and decreased insulin secretion. For example, Nielsen *et al.*⁴⁷ found that a therapeutically relevant dose of CsA (100 ng/mL) increased the residual insulin content of cultured human isolated islets by 59% after a 5-day culture period, whereas the glucose-stimulated insulin release was reduced by 36%. In addition, treatment of mice with CsA (25 mg/kg) for 11 days caused a marked fall in pancreatic insulin content, although plasma glucose and plasma insulin concentrations were unchanged.⁴⁸

In the present study, two dogs had unexpectedly high 24 h postmedication trough CsA concentrations. The cause of the high serum concentrations of CsA in these two dogs, which was in marked contrast to the other 14 dogs, may be explained by individual variation in CsA metabolism. Such interindividual differences in CsA metabolism have been described in other human and canine studies.^{49–51} Marchetti *et al.*⁴⁹ reported variable concentrations of CsA in whole blood of dogs treated with CsA, and van Schilfgaarde *et al.*¹⁸ found that CsA concentrations varied between 218 and 2191 ng/mL in dogs that had previously been subjected to segmental pancreatic autotransplantation.

Further studies are required to assess whether treatment with microemulsified CsA at standard doses has a residual impact on glucose homeostasis in dogs once treatment has ceased. In addition, as our study only examined the impact of 6 weeks of CsA, further studies are also required to examine possible additional effects in dogs that are treated for a longer period. Finally, our study examined the effects of CsA treatment on the insulin and glucose concentrations following a GST immediately before medication; it is unclear whether CsA has differing effects on glucose homeostasis at earlier time points following medication.

In summary, we have shown that administration of CsA in a microemulsion formulation at the licensed dosage produces a disturbance of glucose metabolism in dogs with atopic dermatitis. The mechanism(s) by which

CsA produces these effects is unclear, but this study suggests that reduced insulin production may be important. These data may be relevant to clinicians when considering the suitability of CsA therapy for atopic dogs which already have impaired glucose homeostasis.

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Résumé Les effets de la ciclosporine A (CsA) sur l'homéostasie du glucose ont été étudiés chez 16 chiens atteints de dermatite atopique (DAC) en mesurant les concentrations en glucose plasmatique, en fructosamine sérique et en insuline ainsi que les concentrations d'insuline et de glucose suivant un test de stimulation au glucagon (GST), avant et six semaines après un traitement de CsA à 5 mg/kg une fois par jour. Tous les chiens ont finalisé l'étude. A la suite du traitement à la CsA, les concentrations moyennes en fructosamine sérique étaient significativement plus élevées (prétraitement 227.5 $\mu\text{mol/L}$; post-traitement 246.5 $\mu\text{mol/L}$; $P = 0.001$; valeurs de référence 162–310 $\mu\text{mol/L}$). A partir des analyses des aires sous les courbes temps-concentration (AUC) pré- et post-traitement, les concentrations de glucose plasmatique étaient significativement plus élevées (AUC avec une correction des données de base de 27.0 mmol/min de plus ; $P = 0.017$) et des concentrations en insuline sérique significativement plus basses (AUC avec une correction des données de base de 291.5 $\mu\text{IU/min/mL}$ de moins ; $P = 0.062$) suivant le traitement à la

CsA. Un pic de concentrations de glucose après GST était significativement plus élevé suivant le traitement de CsA (10.75 mmol/L *versus* 12.05 mmol/L, $P = 0.021$), mais il n'y avait aucune différence significative dans les pics d'insuline sérique (52.0 μ IU/mL *versus* 35.0 μ IU/mL; $P = 0.052$). Il y avait une corrélation négative entre l'AUC d'insuline et les creux de concentrations de CsA sériques (-0.73 ; $P = 0.003$). L'administration de CsA aux chiens atopiques mène à des déséquilibres de l'homéostasie du glucose. La signification clinique n'est pas claire mais elle doit être prise en compte pour la mise sous traitement de CsA des chiens ayant déjà de tels troubles.

Resumen Se investigo el efecto de la ciclosporina A (CsA) en la homeostasis de glucosa en 16 perros con dermatitis atópica (cAD) mediante la determinación de la glucosa en plasma, fructosamina en suero y las concentraciones de insulina, así como concentraciones seriadas de insulina y glucosa tras una prueba de estimulación con glucagón (GST), antes y 6 semanas después del tratamiento con CsA a 5 mg/kg una vez al día. Todos los perros completaron el estudio. Tras el tratamiento con CsA, las concentraciones medias de fructosamina fueron significativamente mayores (pre- tratamiento 227,5 μ mol/L; post-tratamiento 246,5 μ mol/L; $P = 0,001$; rango de referencia 162–310 μ mol/L). Basado en el análisis de las áreas bajo las curvas de concentración-tiempo (AUC) pre y post-tratamiento, las concentraciones en el plasma de glucosa fueron significativamente mayores (AUC con corrección de nivel basal 27,0 mmol/min mayor; $P = 0.017$) y las de insulina en el suero fueron significativamente menores (AUC con corrección de nivel basal 291,5 μ IU/min/ml menor; $P = 0,062$) tras el tratamiento con CsA. Las concentraciones mayores de glucosa tras GST fueron significativamente mayores tras el tratamiento con CsA (10,75 mmol/L *versus* 12,05 mmol/L, $P = 0,021$), pero no hubo diferencia significativa en los niveles más altos de insulina (52,0 μ IU/mL *versus* 35,0 μ IU/mL; $P = 0,052$). Hubo una correlación negativa entre el AUC de la insulina y los niveles en suero de CsA ($-0,73$; $P=0,003$). La administración de CsA a perros con AD conlleva alteraciones en la homeostasis de la glucosa. El significado clínico de este hallazgo no esta claro, pero se debe tener en cuenta cuando se considera el tratamiento con CsA en perros que ya presentan una alteración previa.

Zusammenfassung Die Auswirkung von Ciclosporin A (CsA) auf die Homöostase der Glukose wurde bei 16 Hunden mit atopischer Dermatitis (cAD) mittels Bestimmung der Plasma-Glukose, des Serum-Fruktosamins und der Insulinkonzentrationen, sowie mittels fortlaufender Insulin- und Glukosekonzentrationen nach einem Glukagon Stimulationstest (GST) vor und 6 Wochen nach CsA Behandlung mit einer Dosis von einmal täglich 5 mg/kg untersucht. Alle Hunde beendeten die Studie. Nach der CsA Behandlung waren die mittleren Serum-Fruktosamin Konzentrationen signifikant höher (vor der Behandlung 227,5 μ mol/L; nach der Behandlung 246,5 μ mol/L; $P = 0,001$; Normalwerte 162–310 μ mol/L). Basierend auf einer Analyse der Flächen unter den Konzentrations-Zeitkurven (AUC) vor und nach CsA-Behandlung, waren die Plasma-Glukose Konzentrationen nach CsA Behandlung signifikant erhöht (AUC nach Baseline-Korrektur um 27,0 mmol/min höher; $P = 0,017$) und Serum Insulinkonzentrationen signifikant vermindert (AUC nach Baseline-Korrektur um 291,5 μ IU/min/mL niedriger; $P = 0,062$). Die Peak Glukose-Konzentrationen nach dem GST waren signifikant höher nach der CsA Behandlung (10,75 mmol/L *versus* 12,05 mmol/L, $P = 0,021$), aber es gab keinen signifikanten Unterschied beim Höchstwert des Serum Insulins (52,0 μ IU/mL *versus* 35,0 μ IU/mL; $P = 0,052$). Es bestand eine negative Korrelation zwischen Insulin AUC und den niedrigsten Serum CsA Konzentrationen ($-0,73$; $P = 0,003$). Die Verabreichung von CsA bei Hunden mit AD führt zu Störungen in der Homöostase der Glukose. Die klinische Signifikanz dieser Tatsache ist unklar, sollte aber beachtet werden, wenn eine CsA Behandlung bei Hunden in Erwägung gezogen wird, die bereits eine derartige gesundheitliche Beeinträchtigung haben.

要約 シクロスポリン (CsA) のグルコース恒常性への影響を、16 頭の犬アトピー性皮膚炎の犬を用いて、CsA を 5 mg/kg 1 日 1 回投与する前、および投与 6 週後に、血糖値、フルクトサミン、投与前のインスリン濃度、ならびにグルカゴン刺激試験 (GST) 後のインスリンと血糖値を測定することによりしらべた。すべての犬が試験を終了した。CsA 治療後、血清フルクトサミン濃度は有意に高くなっていた (治療前 227.5 μ mol/L; 治療後 246.5 μ mol/L; $P = 0.01$; 参考値 162–310 μ mol/L)。CsA 投与前、投与後の濃度曲線下面積 (AUC) 分析に基づくと、CsA 投与後に血糖値は有意に上昇しており (AUC はベースラインを 27.0 mmol/min より大きい場合補正した; $P = 0.017$)、血清インスリン濃度は有意に低下していた (AUC はベースラインを 291.5 μ IU/min/mL より低い場合補正した; $P = 0.062$)。GST 後の血糖値のピークは CsA 投与後に有意に高かった (10.75 mmol/L に対して 12.05 mmol/L, $P = 0.021$)。しかし血清インスリン濃度のピークに有意な違いは認められなかった (52.0 μ IU/mL に対して 35.0 μ IU/mL; $P = 0.052$)。インスリン AUC と血清 CsA 濃度の間には負の相関がみられた (-0.73 ; $P = 0.003$)。CsA を AD の犬へ投与するとグルコース恒常性が障害を受ける。この臨床的な意義は明らかではないが、グルコース恒常性に障害を有する犬に CsA による治療を検討するときは考慮を要する。