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Final report

A novel therapeutic option for treating horses with insulin dysregulation and preventing laminitis

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Part 1: Detailed summary

Objective/hypothesis: Compare short-term effects of canagliflozin (0.6 and 1.2 mg/kg) vs placebo on the postprandial glucose and insulin responses as well as the effects on body weight, triglyceride and electrolyte concentrations, glucagon secretion, β-cell function and blood pressure in ID horses.
Horses: 42 privately owned insulin dysregulated horses (study was planned for 45 horses)
Methods: A multicenter, randomized, double-blind, placebo-controlled parallel design study. The horses were randomized (ratio 1:1:1) to either once daily oral treatment with canagliflozin (0.6 or 1.2 mg/kg) or placebo. The study consisted of an initial 5-day period to obtain baseline data, a 3-week double-blind treatment period at home, and a 5-day follow-up period similar to the baseline period but with continued double-blind treatment. Horses were subjected to an oral sugar test, a meal tolerance test, a graded glucose infusion test and measurement of indirect blood pressure on each visit. The study was executed as planned.
Results: Treatment with canagliflozin efficiently reduced the postprandial insulin response compared to placebo. Our results showed that treatment with canagliflozin decreased the postprandial insulin response by two major mechanisms: decreased glycemic response and decreased β-cell responsiveness to glucose. The short-term treatment was well tolerated, and no clinical adverse effects were identified over the 3-week treatment period.
Potential for implementation in the practical horse sector: SGLT2 inhibitors appear to be the most efficient pharmacological treatment in decreasing excessive postprandial insulin response in ID horses thereby preventing laminitis, however long-term studies are urgently needed.

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Part 2: Main report (max. 10 pages)

Introduction

Horses with insulin dysregulation (ID) respond to intake of non-structural carbohydrates (NSC) with excessive postprandial hyperinsulinemia,[1,2] which can cause laminitis.[3] Therefore, reducing excessive hyperinsulinemia is a cornerstone in preventing laminitis in these horses. The current strategy for reducing postprandial hyperinsulinemia is to keep the intake of NSC low and, when appropriate, improve tissue sensitivity by promoting weight loss and promoting exercise.[4] However, there is a need for complementary pharmacological treatments that efficiently will decrease the postprandial hyperinsulinemia, especially in cases that are refractory to dietary management. Pioglitazone has recently been shown to decrease the insulin response during an oral sugar test (OST) in ID horses, but the efficacy is low.[5] Metformin hydrochloride has low oral bioavailability in the horse[6] and its efficacy in decreasing excessive postprandial insulin responses in naturally-occurring ID has recently been questioned.[7]

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a new treatment option for human adults with type 2 diabetes (T2DM). These drugs reduce the hyperglycaemia in T2DM patients by therapeutic inhibition of glucose reabsorption in the proximal tubule in the kidneys resulting in glucosuria.[8] The increase in urinary glucose excretion is partly balanced by increased glucose production resulting in improved glycaemic control with low risk of hypoglycaemia.[9] Decreasing postprandial plasma glucose concentrations and thereby reducing the postprandial insulin response may offer a novel therapeutic option for treating excessive hyperinsulinemia in ID horses.

Recently, the SGLT2 inhibitor velagliflozin, was shown to effectively reduce the postprandial insulin response in ID horses fed a challenge diet high in NSC. The treated horses did not develop laminitis whereas 36% of the untreated horses did develop laminitis on the same diet.[10] In a study of 16-week duration, velagliflozin was shown to be well tolerated without any side effects such as urinary tract infections, hypoglycaemia and negative energy balance.[11] In comparison with humans where treatment with SGLT2 inhibitors result in maintained body weight loss,[8] 16 weeks of treatment with velagliflozin had no effect on horses' weight.[11] The SGLT2 inhibitor velagliflozin is, however, not a registered drug on the market. Canagliflozin, a commonly prescribed SGLT2 inhibitor for humans with T2DM, might act as an off-label alternative to velagliflozin.

Therefore, the first objective of this study was to compare the effects of two dosages of canagliflozin versus placebo on the glucose and insulin responses after an oral sugar test (OST) and a meal tolerance test (MTT) in horses with ID. The second objective was to determine if canagliflozin causes decrease in body weight, increase in triglycerides, decrease in blood pressure and disturbances in serum electrolytes. The third objective was to evaluate if canagliflozin causes changes in β-cell sensitivity to glucose or disturbed glucagon secretion.

Material and methods

Study design

This was a multi-center, randomized, double-blind, placebo-controlled, parallel-design study in horses with ID. Privately owned horses with ID were randomized with a 1:1:1 allocation ratio using an online web-based randomization service (www.randomizer.org) to receive either once-

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daily oral canagliflozin (0.6 mg/kg or 1.2 mg/kg) or placebo. The staff conducting the trial and performing the analyses as well as the horse owners were blinded for the randomization throughout the trial.

The study consisted of an initial 5-day period to obtain baseline data, a 3-week double-blind treatment period at home and a 5-day follow-up period similar to the initial baseline period but with double-blind treatment. The baseline and follow-up periods were conducted at two centers (the Equine Clinics at either the Swedish University of Agricultural Sciences (SLU) or the Norwegian University of Life Science (NMBU).

Horse owners were instructed to keep the feeding constant 1 month prior to and over the whole study period by daily weighing of the feed on a scale. They were also instructed to maintain the horse on the same batch of roughage at least 2 weeks prior to the study and over the whole study period. The horses' exercise as well as the turnout time in a dirt- or sand paddock were also kept constant. All horse owners provided written informed consent.

Enrollment criteria

Client-owned horses and ponies previously diagnosed with ID were enrolled. The diagnosis of ID was based on blood samples obtained by referring veterinarians during an OST between 60 and 90 minutes after oral administration of Dan Sukker glucose syrup.[12] Horses with insulin concentrations > 100 µIU/mL were eligible to participate in the study. Horses were excluded if they were < 4 years of age, had an ongoing acute episode of laminitis based on clinical examination or had clinical evidence of pituitary pars intermedia dysfunction including assessment of EDTA plasma ACTH concentrations adjusted for season. Additional exclusion criteria included treatment with drugs and access to grass pasture for at least 1 month before enrollment and systemic disease other than ID. Mares were excluded if they were pregnant or lactating.

Experimental protocol

The horses arrived to either SLU or NMBU, initially for a 5-day visit to obtain baseline data and a second time for a 5-day follow up with double-blind treatment after 3 weeks of treatment at home. On both clinical visits, the horses were allowed to acclimatize to the environment where the experiment was to take place for 2 days. Horses were maintained on their regular diet and fed the daily amount divided into 4 meals. They had daily access to a sand paddock but were kept in a stall at night and during the experimental procedures.

The second day on both clinical visits, clinical examination was performed and body condition score (BCS) and cresty neck score (CNS) were obtained. In addition, an intravenous catheter was inserted into one of the jugular veins under local anesthesia (EMLA, AstraZeneca AB, Södertälje, Sweden). On both clinical visits, feed was withheld in the morning of the third day, the horses' body weight were measured with a calibrated scale and an OST started at 7 a.m. Baseline sampling for the OST was performed via the jugular catheter within 10 minutes before oral administration of 0.5 ml Dan Sukker glucose syrup/kg body weight. Blood samples were obtained via the jugular catheter at 15, 30, 60, 90, 120, 150, 180, 210, 240, 270 and 300 minutes after oral sugar administration.

The fourth day on both clinical visits, the horses' blood pressure was determined at 6 a.m. using an indirect oscillometric device (Memo Diagnostic High Definition Oscillometry Monitor; S + B medVET GmbH) applied to the middle of the coccygeal artery. A MTT was performed at 7 a.m. where the horses' own hay or haylage was fed (0.4 kg roughage on dry matter basis

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per 100 kg of body weight). Sampling for the MTT was performed as for the OST with the exception of the 15-minute sampling, which was omitted. After the MTT, a second intravenous catheter was inserted into the contralateral jugular vein under local anesthesia (EMLA, AstraZeneca AB, Södertälje, Sweden).

The fifth day on both clinical visits a graded glucose infusion (GGI) test for assessment of the horses' β-cell function was performed. A 240-minute GGI was initiated as a stepped intravenous infusion with 20 % dextrose (Glucose Fresenius Kabi 200 mg/ml) at a rate of 0.4 mg/kg/min, followed by 0.8, 1.2, 1.6, 2.4 and 3.2 mg/kg/min. Each infusion period lasted 40 min. Blood samples were collected from the contralateral jugular catheter 10 and 1 min before start of the infusion and then at 10, 20, 30, 40 min into each 40-minute period.

After conclusion of the GGI, the jugular catheters were removed and the feeding protocol resumed. Blood was transferred to vacutainer blood tubes containing lithium heparin, EDTA or no additive as appropriate. Samples without additive were allowed to clot before centrifugation whereas samples with additive were centrifuged within 5 minutes. Plasma or serum was harvested and immediately frozen at -80°C. Plasma insulin levels were analyzed in duplicate using an equine-optimized ELISA (Equine Insulin ELISA; Mercodia AB, Uppsala, Sverige). Plasma glucose levels were analyzed as single samples using an automated clinical chemistry analyzer (YSI 2500 glucose/lactate analyzer; Yellow Springs Instruments, Yellow Springs, USA). Plasma glucagon concentrations were analyzed in duplicate using an ELISA (Glucagon ELISA – 10 µL; Mercodia AB, Uppsala, Sverige). Triglycerides and electrolytes (Na^+, K^+ and Cl^-) were analyzed at the clinical pathology departments within SLU and NMBU using automated analyzers used in routine diagnostics.

Outcomes

Primary endpoints were determined by an OST and a MTT and included change from baseline to the end of treatment for the area under the plasma insulin vs time curve (insulin $AUC_{0\text{-}300}$). The secondary endpoints were the corresponding values for area under the plasma glucose vs time curve (glucose $AUC_{0\text{-}300}$). Additional secondary endpoints were the difference from baseline to the end of treatment for serum triglycerides, serum electrolytes (Na^+, K^+ and Cl^-) and body weight. Exploratory endpoints included change in β-cell responsiveness to glucose from baseline to the end of treatment determined from the dose response curves from the GGI, indirect blood pressure and glucagon secretion during the postprandial phase during the OST.

Statistical method

The insulin $AUC_{0\text{-}300}$ and glucose $AUC_{0\text{-}300}$ was calculated using the trapezoidal rule.[13] The slope of the linear relationship between the increases in glucose vs insulin concentrations during the GGI was used as an index of the β-cell responsiveness to glucose.[14-16]

The primary, secondary and exploratory endpoints were analyzed using analysis of covariance (ANCOVA) with treatment (placebo vs canagliflozin) as fixed factor and the corresponding baseline as a continuous covariate to adjust for baseline values and center as random factor.[17] The full model included an interaction term between the covariate and the treatment. The interaction term was removed from the model if not significant and data were analyzed with an ANCOVA model with equal slopes. If the interaction between the covariate and the treatment was significant, the interaction was included in the model, thus concluding nonparallel lines necessary to adequately describe the data. Comparisons of the treatment effect between canaglifozin and placebo were then performed at three levels of the covariate (baseline data):

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at the mean - 1 SD, mean and mean + 1 SD. Full description of the statistical methods and assumptions are previously reported.[18]
Comparison between time points or between treatments at different levels of the covariate were performed using Tukey-Kramer post hoc test. Values where $P < 0.05$ were considered as statistically significant. All statistical analyses were performed using JMP Pro version 18.0.0 (SAS Institute Inc, Cary, NC).

Results and discussion

Horses

Of the 42 horses randomized to treatment, 41 horses completed the study (canagliflozin 0.6 [n=14], canagliflozin 1.2 [n=14] and placebo [n=13]). The study included a mixed breed of horses (pony breeds (n = 23), Icelandic horses (n = 12), and warmblood or coldblooded breeds (n = 6). Horses and ponies will hereafter in this report be termed collectively as horses. Baseline clinical characteristics of both groups such as age, sex, weight, BCS, CNS, and frequency of previous episodes of laminitis were well matched between the two groups (data not shown).

Postprandial insulin responses

After oral administration of glucose syrup, the postprandial insulin response over time was reduced with canagliflozin compared to placebo (main effect of treatment $P < .0001$). Insulin $AUC_{0\text{-}300}$ significantly decreased at 3 weeks with canagliflozin but there was no difference between the two dosages of canagliflozin (Figure 1A). The geometric LS mean insulin responses ($AUC_{0\text{-}300}$) for canagliflozin treated horses after an OST were 40.1% (25.8 – 62.8%) (canagliflozin 0.6) or 30.7% (19.4 – 48.8%) (canagliflozin 1.2) of the geometric LS mean insulin response ($AUC_{0\text{-}300}$) for the placebo treated horses, i.e. 59.9% and 69.3% reduction in insulin responses with canagliflozin treatment for canagliflozin 0.6 and 1.2 respectively.

After a standardized MTT with the horses own hay or haylage (with low NSC content < 10%), the postprandial insulin response over time was reduced with canagliflozin compared with placebo (main effect of treatment $P < .0001$). Insulin $AUC_{0\text{-}300}$ significantly decreased at 3 weeks with canagliflozin treatment. There was a larger decrease with 1.2 compared to 0.6 mg/kg canagliflozin treatment ($P = .02$) (Figure 2A). The geometric LS mean insulin responses ($AUC_{0\text{-}300}$) for canagliflozin treated horses after a MTT were 45.0% (32.3 – 62.7%) (canagliflozin 0.6) or 30.6% (21.9 – 42.9%) (canagliflozin 1.2) of the geometric LS mean insulin response ($AUC_{0\text{-}300}$) for the placebo treated horses, i.e. 55.0% and 69.4% reduction in insulin responses with canagliflozin treatment for canagliflozin 0.6 and 1.2 respectively.

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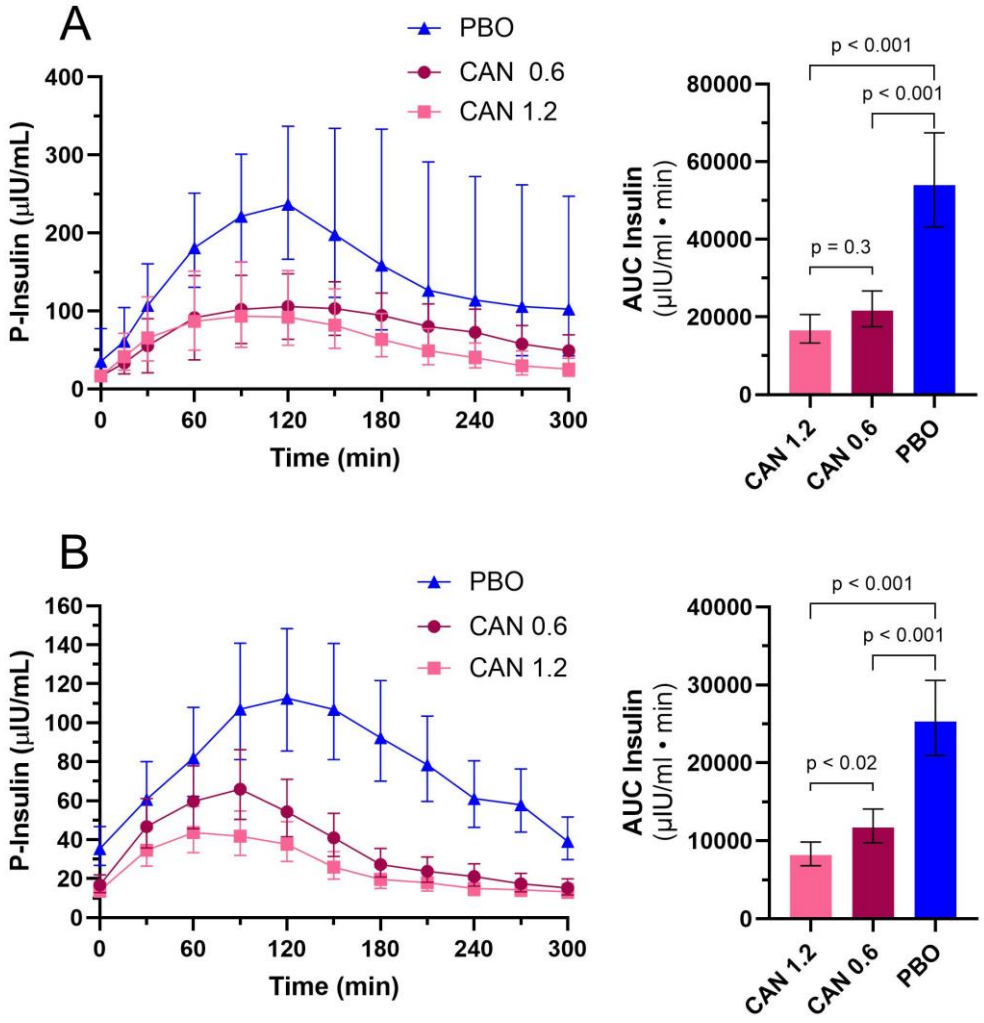

Figure 1. Geometric least square mean and 95% confidence interval concentration-time profiles for plasma insulin from before to 300 minutes after an oral sugar test (0.5 mL/kg dose of glucose syrup; Dan Sukker) (**A**) or after an standardized meal tolerance test with the horses' own hay or haylage (0.4 kg dry matter roughage per 100 kg of body weight) (**B**). The geometric least square means and 95% confidence interval for area under the curve (overall insulin responses) are displaced to the right. Placebo (PBO), canagliflozin 0,6 mg/kg (CAN 0.6) and canagliflozin 1.2 mg/kg (CAN 1.2).

Postprandial glucose responses

The ANCOVA for glucose $AUC_{0\text{-}300}$ from the OST and MTT demonstrated covariate by treatment interaction (P = .0005 and P = .03 respectively). Treatment with canagliflozin (0.6 or 1.2 mg/kg) did only show a treatment effect for canagliflozin at increased values for baseline glucose $AUC_{0\text{-}300}$ (detailed data nor shown) for both the OST and the MTT.

Body weight, serum triglycerides, serum electrolytes and indirect blood pressure

Treatment with canagliflozin (0.6 or 1.2 mg/kg) resulted in significantly (P > .005) greater percentage decrease in body weight compared to placebo (Figure 2A).

Canagliflozin increased serum triglyceride concentrations compared to placebo (Figure 2B) with adjusted geometric mean differences > 0.77 mmol/L (P ≤ .006). Post treatment, seven out of 13 placebo horses and all canagliflozin treated horses had serum triglyceride concentrations > 0.50 mmol/L, the laboratory cut off for increased triglyceride concentrations (Clinical Pathology Laboratory, SLU and NMBU). The increase in triglyceride concentrations was not

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accompanied with any clinical signs such as decreased attitude or decrease in appetite. In fact, all horses sustained normal clinical examinations.

Canagliflozin did not cause any changes in serum electrolytes (Na^+, K^+ and Cl^-) ($P > .6$) or in blood pressure (systolic, diastolic and mean arterial pressure) ($P > .2$) compared to placebo.

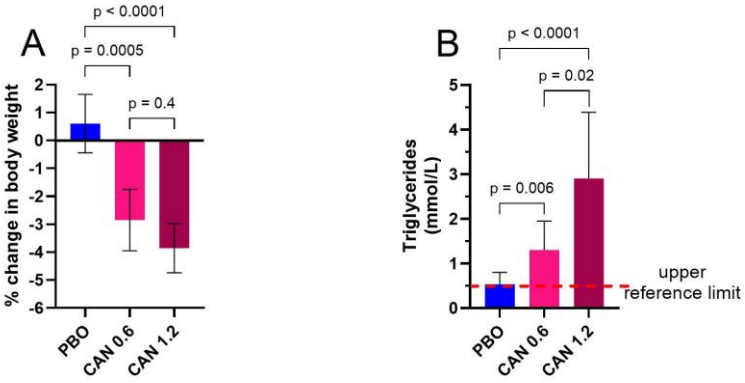

Figure 2. Least square mean percentage change in body weight with 95% confidence interval after treatment with placebo (PBO), canagliflozin 0.6 mg/kg (CAN 0.6) and canagliflozin 1.2 mg/kg (CAN 1.2) (**A**). Geometric least square mean and 95% confidence interval concentration-time profiles for serum triglycerides (**B**).

Postprandial glucagon responses

After oral administration of glucose syrup, the postprandial glucagon response over time was reduced with both placebo and canagliflozin (0.6 and 1.2 mg/kg) treatment. The inhibition in glucagon response during the postprandial phase was more prominent in the placebo horses compared to the canagliflozin 1.2 mg/kg treated horses as expressed by the glucagon $AUC_{0\text{-}300}$ (Figure 3).

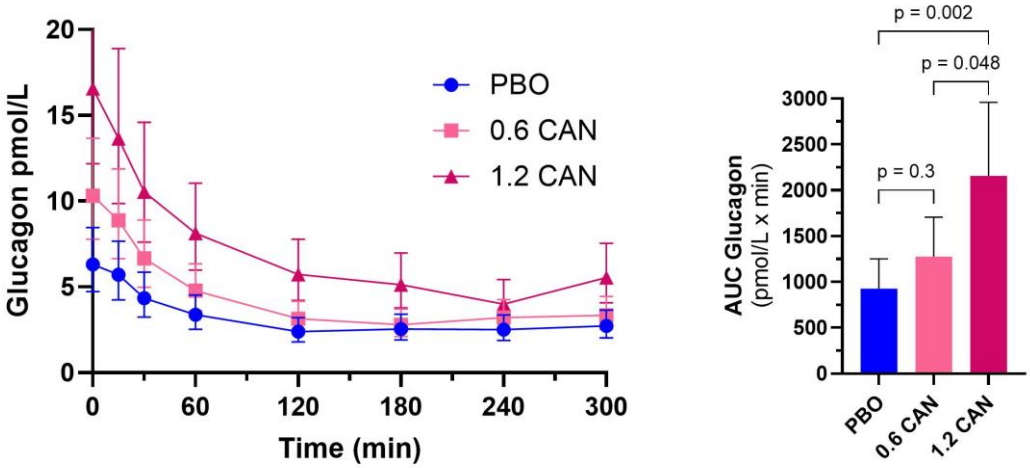

Figure 3. Geometric least square mean and 95% confidence interval concentration-time profiles for plasma glucagon from before to 300 minutes after an oral sugar test (0.5 mL/kg dose of glucose syrup; Dan Sukker). The geometric least square means and 95% confidence interval for area under the curve (overall glucagon responses) are displaced to the right. Placebo (PBO), canagliflozin 0,6 mg/kg (CAN 0.6) and canagliflozin 1.2 mg/kg (CAN 1.2).

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β-cell glucose sensitivity

The β-cell sensitivity to glucose was significantly decreased at 3-weeks of canagliflozin treatment when compared to placebo ($P \leq .0002$), but no difference was found between the two doses of canagliflozin ($P = .98$). The β-cell sensitivity to glucose geometric least square means with 95% confidence interval after treatment was 18.6 (15.3 – 22.5), 19.0 (15.5 – 23.3) and 36.6 (30.2 – 44.4) mIU/mmol for canagliflozin 0.6 mg/kg, canagliflozin 1.2 mg/kg and placebo respectively.

Discussion

Our randomized, placebo-controlled, double-blind study represents the first evidence for the efficacy of canagliflozin in decreasing the hyperinsulinemic response to PO glucose in ID horses. Treatment was well tolerated, and no clinical adverse effects were identified over the 3-week treatment period. Our results showed that treatment with canagliflozin decreased the postprandial insulin response by two major mechanisms: decreased glycemic response and decreased β-cell responsiveness to glucose. This resulted in a very efficient treatment effect, where canagliflozin on average decreased the hyperinsulinemic response by >60% compared with placebo in response to an OST. Currently, the SGLT2 inhibitors appear to be the most efficient pharmacological treatment in decreasing the insulin response to PO sugars in ID horses.

In agreement with previous studies using SGLT2 inhibitors in horses with ID,[10, 11] we observed a significant decrease in the postprandial insulin response after treatment with canagliflozin. Despite decreases in insulin responses, only 39% of the treated horses had normal insulin concentrations after the OST. Our study included horses with moderate and marked ID, and it was therefore not expected that all horses treated with canagliflozin would have normal results on an OST.

Canagliflozin decreased the insulin response to a greater extent compared with the glucose response. In fact, decrease in glucose response following canagliflozin treatment was heterogeneous with treatment effects only seen in horses with initially high glucose responses at baseline. Thus, the high treatment effect of decreasing the insulin response may not be attributed solely to decrease in the glycemic response. This conclusion was supported by a mean decrease of ≥ 67% in the β-cell sensitivity to glucose in canagliflozin compared with placebo-treated horses. In contrast, humans with T2DM have decreased β-cell sensitivity to IV glucose compared with healthy humans as a result of decreased β-cell function.[15] Treatment with SGLT2 inhibitors in humans with T2DM leads to improved β-cell function.[19] This effect has been attributed to a secondary effect of decreased plasma glucose concentration and amelioration of glucotoxicity, and not a direct effect on the β-cell.[20] Interestingly, treatment with SGLT2 inhibitors in ID horses and humans with T2DM affects β-cell sensitivity to glucose in opposite directions. We did not measure C-peptide in our study, and therefore we are not able to assess if the decrease in β-cell sensitivity to glucose after canagliflozin treatment to some extent is explained by an increased clearance rate of insulin. Future studies should investigate in more detail the mechanism by which canagliflozin changes β-cell sensitivity to glucose, because it may be a very important mechanism for decreasing the insulin response in canagliflozin-treated ID horses.

It is well established that human patients receiving SGLT2 inhibitors experience gradual weight loss over time. The weight loss is likely secondary to increased glucose excretion, resulting in caloric loss.[21, 22] In agreement with these studies, the canagliflozin-treated horses in our study experienced weight loss over the treatment period compared to those treated with placebo.

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Although our study did not assess caloric intake over the study period, the horse owners were instructed to cautiously maintain feeding and training as constant as possible for 1 month before and during the treatment period. Interestingly, no changes were seen in the horses' blood pressure or electrolyte concentrations, which further supports that the decrease in body weight was related to loss of calories and not to derangements in the horses' electrolyte or fluid balance.

In agreement with a previous study, where the weight of the ponies remained constant during treatment with SGLT2 inhibitors,[11] treatment with canagliflozin in our study caused an increase in serum triglyceride concentrations despite normal findings on physical examinations of the horses. Despite the weight loss in the canagliflozin-treated horses in our study, no association was found between the increase in triglycerides and the magnitude of weight loss. The SGLT2 inhibitors thus appear to facilitate an increase in serum triglyceride concentrations in ID horses both in stages of normal and negative energy balance. This possibility requires additional studies, because triglycerides already may be increased in horses with ID.[4] In addition, the safety of long-term use of SGLT2 inhibitors in equids is unknown at this time. In agreement with human studies, treatment with SGLT2 inhibitors caused hyperglucagonemia and inappropriate inhibition of postprandial glucagon concentrations in the horses. It is possible that dysregulation of glucagon during both fasting and postprandial conditions contributed to abnormalities in the regulation of the fat metabolism with increase in serum triglycerides as a result.

Conclusions

Taken together, this study indicates that treatment with canagliflozin efficiently decreases the postprandial insulin response in ID horses. The amelioration in insulin response was achieved by a combination of decreased postprandial glucose response and, perhaps most importantly, as a result of decreased β-cell sensitivity to glucose. Canagliflozin did not cause any changes in indirect blood pressure or serum electrolyte concentrations but an increase in serum triglycerides. The increase in triglycerides was not related to the decrease in body weight seen in canagliflozin treated horses. A potential explanation to the derangements in serum triglycerides with canagliflozin treatment could be the concurrent dysregulation of glucagon secretion. These side effects did not cause any clinical signs in the horses, but could be of significance when horses are treated for longer periods. Canagliflozin thus is a promising drug for treatment of ID in horses that requires future long-term studies.

Relevance for the practical horse sector incl. recommendations

Laminitis associated with high insulin concentration is a significant cause of morbidity and mortality in horses, and its management poses a daily challenge in equine practice. The most important current strategy for reducing postprandial hyperinsulinemia is to keep the intake of non-structural carbohydrates low. Unfortunately, excessive hyperinsulinemia is difficult to manage with only dietary restrictions. Cost effective pharmacological options for treating severe hyperinsulinemia and thereby preventing laminitis are therefore highly needed and would be a major breakthrough.

The SGLT2 inhibitors have had a huge impact on the treatment of T2DM in people, and this report suggest they might become similarly important in equine medicine. However, the present study and other similar studies have evaluated the short-term efficacy of SGLT2 inhibitors

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whereas ID horses require long-term treatment. If the evidence from the present study can be corroborated by more robust long-term clinical trials and the safety profile is favorable then the impact on equine welfare could be dramatic. There is also an urgent need for practical guidelines on how to use and monitor the treatment efficacy of SGLT2 inhibitors in equine practice.

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Part 3: Result dissemination

State all result dissemination from the financed project into the appropriate section, including information as indicated in each section. Additional rows can be added to the table.

Scientific publications, *published*	Lindåse S, Nostell K, Forslund A, Bergsten P, Bröjer J. Short-term effects of canagliflozin on glucose and insulin responses in insulin dysregulated horses: A randomized, placebo-controlled, double-blind, study. J Vet Intern Med. 2023 Nov-Dec;37(6):2520-2528. doi: 10.1111/jvim.16906.
Scientific publications, *submitted*	Bröjer J, Hanche-Olsen S, Nostell K, Fintl C, Risnes Hellings I, Lindåse S. Treatment effects of the sodium-glucose cotransporter-2 inhibitor canagliflozin in horses with insulin dysregulation: A short-term randomized, placebo-controlled study.
Scientific publications, *manuscript*	**Part of Elin Svonnis PhD-project:** Svonni E, Lindåse S, Hanche-Olsen S, Nostell K, Fintl C, Risnes Hellings I, Bergsten P, Bröjer J. Effects of canagliflozin on β-cell function in horses with insulin dysregulation: a double-blind randomized placebo-controlled study
Conference publications/ presentations	Bröjer J. 2024. Strategisk behandling av insulindysreglering – att vända frustration till framgång. VETA-dagarna. 16 – 17 mars 2024, Stockholm, Sverige.
	Bröjer J. 2024. Equine metabolic syndrome – new treatment possibilities. Nordic College Equine Dentistry, 18th – 20th January 2024, Malmö, Sweden
	Lindåse S, Nostell K, Hanche-Olsen S, Risnes Hellings I, Fintl C, Bröjer J. Short-term effects of canagliflozin on postprandial glucose and insulin responses – preliminary results from an ongoing randomized, double-blind, placebo-controlled study. Global Equine Endocrinology Symposium 2023.January 3rd – 5th 2023, National Horse Center, Bern, Switzerland
	Bröjer J, Svonni E, Nostell K, Hanche-Olsen S, Risnes Hellings I, Fintl C, Lindåse S Short-term effects of canagliflozin on β-cell function in horses with insulin dysregulation – preliminary results from an ongoing randomized, double-blind, placebo-controlled trial. Global Equine Endocrinology Symposium 2023.January 3rd – 5th 2023, National Horse Center, Bern, Switzerland
Other publications, *media etc.*	**The interest among horse media has been extensive for the project. Below are only a few of these articles listed:**
	Effektiv behandling förebygger fång vid EMS. 12 februari 2024. SLUs kunskapsbank.

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	https://www.slu.se/forskning/kunskapsbank/publicerat/sport--och-sallskapsdjur/hastnotiser/effektiv-behandling-forebygger-fang-vid-ems/
	Drug shows promise in managing insulin dysregulation in horses – study, October 27, 2023, Horsetalk.co.nz. https://horsetalk.co.nz/2023/10/27/drug-promise-insulin-dysregulation-horses-study/
	Integrating SGLT2is into Management of Equine Metabolic Syndrome, April 21, 2023, The Horse, Posted by Stacey. https://thehorse.com/1121710/integrating-sglt2is-into-management-of-equine-metabolic-syndrome/
	Medication Provide Added Protection from Some Horses at Risk of Lamninitis. Kentucky Equine Research. November 29, 2023. https://ker.com/equinews/medications-provide-added-protection-for-some-horses-at-risk-of-laminitis/
	Diabetesmedicin giver nyt håb for heste med forfangenhed Ny undersøgelse viser, at et lægemiddel, der bruges til personer med diabetes-2, også virker til heste. 16 maj 2023. Fritidsmarket. https://www.fritidsmarkedet.dk/artikel/122119-diabetesmedicin-giver-nyt-haab-for-heste-med-forfangenhed
	Diabetesmedicin kan bli möjlig behandling för fångsjuka hästar. 12 april, 2022. Hästsverige. https://hastsverige.se/news/forskning-diabetesmedicin-till-fangsjuka-hastar/
Oral communication, *to horse sector, students etc.*	Behandling av hästar med insulindysreglering. 2024. Redovisning av ett forskningsprojekt finansierat av Stiftelsen Hästforskning. Inspelat föredrag via hippocampus nya mediesatsning. Link not available yet.
	Insulinresistens hos häst - en klinisk utmaning. 13 maj, 2022. Professorsinstallation – föreläsning SLU. https://youtu.be/ryXuCAd5czk
Student theses	*Author/Student, co-authors/supervisors, year, title, type of thesis (doi/link if applicable)*
	Sofia Vigren (supervisor J Bröjer). 2021. Blood glucose and plasma insulin at two different doses of SGLT2- inhibitors in horses diagnosed with equine metabolic syndrome. Master thesis (Examensarbete), Sveriges lantbruksuniversitet, SLU https://stud.epsilon.slu.se/16875/1/vigren_s_210312.pdf
	Ida Ivarsson (supervisors S Lindåse and J Bröjer). 2023. Is the efficacy of treatment with kanagliflozin affected by the severeness of insulin dysregulation in horses with equine metabolic syndrome? Master thesis (Examensarbete), Sveriges lantbruksuniversitet, SLU https://stud.epsilon.slu.se/18696/1/ivarsson_i_230130.pdf
Other	

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