

STANDARD ARTICLE

Influence of endocrine disease on I-lactate concentrations in blood of ponies

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Abstract

Background: Blood I-lactate concentrations are higher in people with developing or established diabetes mellitus and insulin resistance.

Objectives: To investigate whether blood I-lactate concentrations are positively correlated with measures of insulin dysregulation (ID) or increased autumnal ACTH concentrations in ponies.

Animals: Systemically healthy client-owned ponies (n = 101).

Methods: Prospective case-control study. Blood samples were obtained from 101 clinically healthy ponies. Breed, weight, height, and subjective and objective measures of body condition were recorded. Blood I-lactate, glucose, triglyceride, total adiponectin, and ACTH concentrations were measured and an oral sugar test (OST) was carried out. Correlations between blood I-lactate and variables of endocrine health were determined.

Results: Using a seasonal cutoff point of ACTH concentrations ≥ 47 pg/mL, 55 ponies had increased autumnal ACTH concentrations and 45 did not. Using a basal insulin concentration of >50 μ iU/mL, 42 ponies were diagnosed with ID and 58 were not. Using a 60 minutes after OST cutoff point of >45 μ iU/mL, 57 ponies had ID and 37 did not. Blood I-lactate concentrations were significantly lower in obese (average body condition score $\geq 7/9$) compared to nonobese ponies (0.6 mmol/L; range, 0.0-1.9 mmol/L vs 0.8 mmol/L; range, 0.3-2.7 mmol/L; $P = .01$). No other significant correlations were detected. No differences were detected between ponies with and without increased autumnal ACTH concentrations (0.7 mmol/L; range, 0.0-2.7 mmol/L vs 0.7 mmol/L; range, 0.3-1.8 mmol/L; $P = .84$) and with and without ID (0.7 mmol/L; range, 0.3-2.7 mmol/L vs 0.8 mmol/L; range, 0.0-1.6 mmol/L; $P = .63$).

Conclusions and Clinical Importance: Results do not support an effect of endocrine status on I-lactate concentrations in blood of ponies.

KEYWORDS

adiposity, equine, insulin resistance, I-lactate metabolism, pituitary pars intermedia dysfunction

Abbreviations: BCS, body condition score; ID, insulin dysregulation; OST, oral sugar test; PPID, pituitary pars intermedia dysfunction.

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1 | INTRODUCTION

The metabolism of glucose and l-lactate is tightly linked through the Cori cycle. l-Lactate is an important gluconeogenic precursor as it can be converted first into pyruvate and then glucose via gluconeogenesis.¹ The reverse is also possible with glucose being converted into l-lactate from the reduction of pyruvate via lactate dehydrogenase under aerobic or anaerobic conditions.² There is a tight correlation between both metabolites in critically ill people and horses.^{3,4} In critical illness, inflammatory mediator and catecholamine release are responsible for insulin resistance and excessive glycolysis, both contributing to hyperglycemia and hyperlactatemia.⁵ However, endocrine diseases that affect the insulin sensitivity of tissues can also influence glucose and l-lactate metabolism. Adipose tissue is thought to play an important role in supplying l-lactate⁶ and l-lactate is a signaling molecule with autocrine, paracrine, and endocrine-like effects.¹ In people, higher blood l-lactate concentrations occur in association with obesity and type 2 diabetes. Not only are blood l-lactate concentrations higher in patients with type 2 diabetes, but they also predict the occurrence of diabetes.⁷⁻¹¹ In people with diabetes and insulin resistance, hyperinsulinemia leads to increased glycolysis which in turn results in enhanced pyruvate production followed by exaggerated conversion of pyruvate to l-lactate.⁷ l-Lactate concentrations therefore reflect the state of cellular metabolism, and increased concentrations are thought to be an early signal of emerging or established insulin resistance.⁷

While diabetes mellitus is comparatively rare in equids, other endocrine diseases such as pituitary pars intermedia dysfunction (PPID) and insulin dysregulation (ID) are common. Hyperinsulinemia can be a feature of both, PPID and ID. Hyperglycemia and diabetes mellitus can occur as a consequence of PPID and ID in horses.^{12,13} Blood l-lactate concentrations are higher in ponies with gastrointestinal disease when compared to horses but an underlying reason for this finding is not established.¹⁴ It is possible that a decreased sensitivity to insulin, which occurs in ponies,^{15,16} or underlying endocrine diseases could contribute to the increased blood l-lactate concentrations observed in ponies.^{4,14-17} If blood l-lactate concentrations are higher in ponies with endocrine disease compared to ponies without evidence of an endocrine disorder, this might be a useful early marker of developing endocrine disease, similar to people.

The study tested the hypotheses that blood l-lactate concentrations are associated with measures of endocrine disease in ponies and are higher in ponies with increased autumnal ACTH concentrations or ID than in animals with normal endocrine function.

2 | MATERIALS AND METHODS

The Clinical Research Ethics Board of the Royal Veterinary College granted ethical approval for this study. Blood samples from ponies (≤ 148 cm; 14.2 hands) were obtained in autumn as part of an ongoing study (Home Office Project License [70/8195]) into predicting factors for development of laminitis in healthy not previously laminitic ponies.

None of the ponies showed clinical signs of endocrine disease. All ponies were weighed and body condition scores (BCSs) were assigned for 6 different body regions (neck, withers, shoulder, ribs, loin, and tail head) on a 1 to 9 scale as previously described.¹⁸ In brief, the individual descriptors used in the original Henneke score were applied to each region and the corresponding score was recorded for each region separately to account for regional fat deposition. The mean BCS was also calculated.^{19,20} Obesity was defined as a mean BCS $\geq 7/9$.²¹ Blood samples were collected by jugular venepuncture into vacutainers containing sodium heparin, potassium EDTA, or sodium fluoride/potassium oxalate as an anticoagulant for the ongoing research project. Blood l-lactate concentrations were measured immediately after blood collection in heparinized samples using a hand-held point of care analyzer (NovaVet Statstrip Xpress Lactate meter, Nova Biomedical, Waltham, Massachusetts). The analyzer is manufactured for the European market by the same company that produces the Lactate Plus lactate meter (Nova Biomedical) and uses the same technology. The Lactate Plus lactate meter has been validated for use in horses.²² Plasma was chilled immediately to 4°C to 10°C and separated by centrifugation (2000g), divided into 1 mL aliquots, and then stored at -80°C until analysis. Glucose measurements were performed on stored sodium fluoride/potassium oxalate plasma using a standard laboratory analyzer (Beckman Coulter AU680 Chemistry analyzer; High Wycombe, UK). EDTA-anticoagulated plasma ACTH concentrations were also measured using an immunofluorescence assay validated for use in horses.²³ An oral sugar test (OST) was performed by administering 0.3 mL/kg of Karo Light Corn syrup PO.^{24,25} Ponies had access to pasture but were not fed concentrates before the OST. Blood samples were obtained before and 60 minutes after administration. Blood was collected into clot activator vacutainer tubes. Blood was allowed to clot at ambient temperature (approximately 20°C) and serum was separated by centrifugation (2000g) on the day of collection, separated into 1 mL aliquots, kept at -20°C for short-term storage and at -80°C for long-term storage. The time points for blood sampling were chosen as previous studies showed earlier peaks in blood glucose concentrations in ponies than horses.²⁶ Insulin concentrations were measured in serum by radioimmunoassay (MP biomedical assay, MP Biomedicals SARM, Illkirch-Grafenstaden, France) which has been previously investigated in horses.^{27,28} Basal insulin concentrations >50 $\mu\text{U/mL}$ and/or serum insulin concentrations >45 $\mu\text{U/mL}$ 60 minutes after OST were used to diagnose ID.²⁹ A seasonally adjusted ACTH concentration ≥ 47 pg/mL was used as a cutoff point for increased autumnal ACTH concentrations as suggested in a study using the same methodology.³⁰ As second seasonal threshold of ≥ 76 pg/mL, again established using the same methodology, was also investigated.³¹ Animals <1 year of age were excluded from the study. Total adiponectin and triglyceride concentrations were measured in plasma using a commercially available assays.

2.1 | Statistical analysis

Data were analyzed using a commercially available software programme (SPSS version 24 SPSS, Inc, Chicago, Illinois). Normality of the data were assessed using the Shapiro-Wilk test. All data were non-

TABLE 1 Comparison between sex, age, body condition variables, and blood glucose and lactate concentrations in ponies with and without increased autumnal ACTH concentrations (ACTH concentrations >47 pg/mL), insulin dysregulation (ID; basal insulin concentration > 50 μ U/mL and/or t60 insulin concentrations >45 μ U/mL), and obesity (average body condition score [BCS] \geq 7/9)

| | ACTH (pg/mL) | | Basal insulin (μ U/mL) | | Insulin t60 (μ U/mL) | | Average BCS | | P value | | | |
|---|----------------------------|-----------------------------|-----------------------------|-----------------------------|----------------------------|---------|----------------------------|-----------------------------|---------|-----------------------------|-----------------------------|------------|
| | <47 pg/mL | \geq 47 pg/mL | P value | \leq 50 μ U/mL | >50 μ U/mL | P value | \leq 45 μ U/mL | >45 μ U/mL | | P value | <7/9 | \geq 7/9 |
| Average BCS | 6.2 (4.2-8.0; n = 45) | 5.7 (3.7-8.2; n = 55) | .13 | 5.7 (4.0-7.7; n = 85) | 6.7 (3.7-8.2; n = 15) | .007 | 5.6 (4.0-7.3; n = 37) | 6.0 (3.7-8.2; n = 57) | .08 | 5.4 (3.7-6.3; n = 74) | 7.0 (6.5-8.2; n = 27) | NA |
| Age | 10 (5-24; n = 43) | 13 (5-27; n = 51) | .22 | 10 (5-27; n = 81) | 11 (6-26; n = 13) | .79 | 10 (5-27; n = 35) | 13 (6-26; n = 53) | .26 | 10 (5-27; n = 72) | 11 (7-19; n = 23) | .71 |
| Weight (kg) | 397 (223-570; n = 45) | 336 (77-566; n = 55) | .006 | 355 (77-570; n = 85) | 374 (168-566; n = 15) | .63 | 370 (77-570; n = 37) | 354 (163-566; n = 57) | .51 | 339 (77-546; n = 74) | 424 (168-570; n = 27) | .001 |
| Height (cm) | 138 (105-149; n = 45) | 132 (79-148; n = 55) | .04 | 135 (79-149; n = 85) | 132 (103-145; n = 15) | .49 | 139 (79-149; n = 37) | 132 (100-149; n = 57) | .21 | 132 (79-149; n = 74) | 138 (103-149; n = 27) | .1 |
| I-Lactate concentration (mmol/L) | 0.7 (0.3-1.8; n = 45) | 0.7 (0-2.7; n = 55) | .84 | 0.7 (0.0-2.7; n = 85) | 0.7 (0.5-1.9; n = 15) | .97 | 0.8 (0-1.6; n = 37) | 0.7 (0.3-2.7; n = 57) | .63 | 0.8 (0.3-2.7; n = 74) | 0.6 (0-1.9; n = 27) | .01 |
| Glucose concentration (mmol/L) | 4.6 (3.9-5.7; n = 45) | 4.6 (4.0-5.4; n = 55) | .69 | 4.5 (3.9-5.7; n = 85) | 4.8 (4.3-5.4; n = 15) | .001 | 4.5 (3.9-5.4; n = 37) | 4.6 (4.0-5.7; n = 57) | .02 | 4.6 (3.9-5.5; n = 74) | 4.7 (3.9-5.7; n = 27) | .089 |
| ACTH concentration | 39 (22-46; n = 45) | 82 (47-506; n = 55) | NA | 46 (22-249; n = 85) | 102 (42-506; n = 15) | .001 | 45 (22-151; n = 37) | 52 (35-472; n = 57) | .01 | 51 (22-506; n = 73) | 50 (27-155; n = 27) | .86 |
| Basal insulin (μ U/mL) | 26 (4-145; n = 45) | 32 (8-390; n = 55) | .31 | 26.3 (3.8-48.3; n = 85) | 66 (51-390; n = 15) | NA | 23 (8-38; n = 37) | 36 (4-390; n = 57) | <.001 | 26.4 (3.8-104; n = 73) | 36.6 (12.8-390; n = 27) | .004 |
| Insulin t60 (μ U/mL) | 47 (9-280; n = 45) | 60 (16-482; n = 50) | .007 | 47.1 (8.8-180; n = 79) | 172 (51-482; n = 15) | <.001 | 31 (9-45; n = 37) | 76 (46-482; n = 57) | NA | 50.6 (8.8-228; n = 68) | 72.1 (9.6-482; n = 26) | .06 |
| Adiponectin concentration (μ g/mL) | 17 (0.5-48; n = 41) | 16 (0.2-51; n = 53) | .78 | 16.8 (0.2-51; n = 80) | 14.6 (1.1-51; n = 14) | .92 | 16 (0.7-43; n = 35) | 16 (0.2-51; n = 53) | .42 | 17.2 (0.22-50.9; n = 69) | 12.5 (0.7-50.5; n = 25) | .15 |
| Triglyceride concentration (mmol/L) | 0.34 (0.11-6.3; n = 41) | 0.34 (0.08-17.3; n = 53) | .94 | 0.34 (0.08-17.3; n = 80) | 0.33 (0.11-1.3; n = 14) | .84 | 0.31 (0.23-1.2; n = 35) | 0.35 (0.08-17.3; n = 53) | .58 | 0.34 (0.08-17.3; n = 69) | 0.34 (0.09-1.85; n = 25) | .65 |

Note: All ponies diagnosed with ID based on basal insulin measurements were also positive for ID at t60. Insulin concentration was measured 60 minutes (t60) after administration of 0.3 mL/kg Karo Light Corn syrup. All data were non-normally distributed and results are shown as median (minimum-maximum). Groups were compared by Mann-Whitney U test and significance was set at $P \leq .05$.

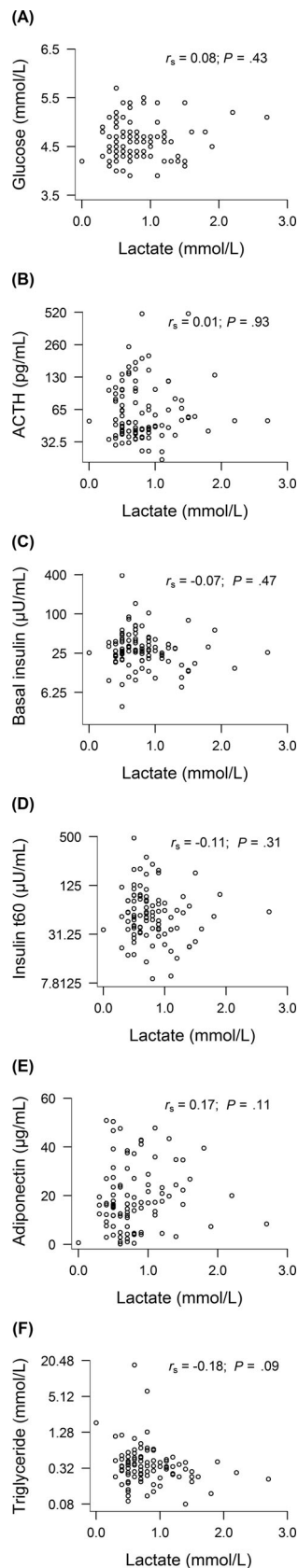


FIGURE 1 Scatter plots showing I-lactate concentrations (x-axis) and measures of endocrine health (y-axis; A-F). The y-axis is shown in a log scale in (B), (C), (D), and (F). Insulin concentration was measured 60 minutes (t₆₀) after administration of 0.3 mL/kg Karo Light Corn syrup. Results of a bivariate Spearman's correlation (*r*) are included in the corresponding graphs. Statistical significance was set at $P \leq .05$

normally distributed and are expressed as median and range (minimum to maximum) and numbers and percentages for categorical data. Blood I-lactate concentrations were compared between obese and lean ponies and between ponies with and without increased autumnal ACTH concentrations and with and without ID. To account for the inherent difficulties with using single cutoff points, blood I-lactate and glucose concentrations were also compared between the first and fourth quartiles of ACTH and insulin t₆₀ concentrations to capture possible difference between the extreme cases. Comparison between groups was done by Mann-Whitney *U* test (non-normally distributed continuous variables). The correlation between blood I-lactate and glucose, triglyceride, total adiponectin and ACTH concentrations and basal and t₆₀ insulin concentrations were evaluated using bivariate Spearman's correlation (*r*) and scatter plots were generated. Statistical significance was set at $P \leq .05$.

3 | RESULTS

One hundred and one ponies comprised of 68 geldings and 33 mares with a median age of 11 years (range, 5-27 years) were included in the study. The median BCS was 6 (range, 3-8). All regional BCSs were either the same as the average BCS or 1 score above or below; only 1 pony deviated by 2 scores from the average (average BCS 7; regional score neck 5 and ribs 9). Blood I-lactate concentrations and measures of endocrine status are displayed in Table 1; results of correlations between blood I-lactate concentrations and these variables are displayed in Figure 1. Blood I-lactate concentrations did not correlate with any of the investigated variables. All ponies diagnosed with ID based on basal insulin measurements were also positive at for ID at t₆₀. Correlations between blood I-lactate concentrations, age, and average BCS in these ponies have been published previously.³² Correlation results did not differ when regional or the average BCSs were used. Blood I-lactate concentrations were statistically significantly lower in obese ponies compared to nonobese animals (0.6 mmol/L; range, 0.0-1.9 mmol/L vs 0.8 mmol/L; range, 0.3-2.7 mmol/L; $P = .01$). Median blood I-lactate concentrations for both groups remained within the reference range and the biological relevance of this finding is questionable. No significant differences were detected between ponies with and without increased autumnal ACTH concentrations and with and without ID (Table 1). Increasing the ACTH threshold to ≥ 76 pg/mL for the diagnosis of increased autumnal ACTH concentrations did not change the results for blood I-lactate concentrations (0.7 mmol/L [0.0-2.7 mmol/L] vs 0.7 mmol/L [0.3-1.9 mmol/L]; $P = .28$). Blood I-lactate concentrations were also not significantly different between the first and fourth quartiles of ACTH concentrations (0.7 mmol/L [0.3-1.3 mmol/L] vs 0.7 mmol/L [0.3-1.9 mmol/L]; $P = .82$) and insulin t₆₀ concentrations (0.8 mmol/L [0-1.5 mmol/L] vs 0.65 mmol/L [0.3-1.9 mmol/L]; $P = .29$). Significant differences for glucose concentrations were detected between the extreme quartiles of ACTH (4.4 mmol/L [3.9-5.5 mmol/L] vs 4.7 mmol/L [4.0-5.4 mmol/L]; $P = .03$) and insulin t₆₀ concentrations (4.3 mmol/L [3.9-5.4 mmol/L] vs 4.8 mmol/L [4.2-5.4 mmol/L]; $P = .002$). The median ACTH and insulin t₆₀ concentration of the first quartile were 36 pg/mL

(22-40 pg/mL) and 25 μ U/mL (9-35 μ U/mL) and 136 pg/mL (96-506 pg/mL) and 117 μ U/mL (82-482 μ U/mL) for the fourth quartile.

4 | DISCUSSION

The study did not identify any correlation between blood I-lactate concentrations and the investigated measures of endocrine health and blood I-lactate concentrations were not different between ponies with and without increased autumnal ACTH concentrations and with and without ID. In type 2 diabetic patients, I-lactate concentrations are positively associated with body weight, body mass index, triglyceride and insulin concentrations and negatively associated with adiponectin concentrations.⁶ There is a decreased insulin sensitivity in overweight and obese horses and ponies and also in a subset of animals with PPID.^{33,34} A similar association between obesity, ID, and increased blood I-lactate concentrations could therefore be present in equids leading to the hypotheses that blood I-lactate concentrations are higher in ponies with increased autumnal ACTH concentrations or evidence of ID and would correlate with measures of endocrine health.^{35,36} However, contrary to findings in people, a negative correlation between I-lactate concentrations and average BCS³² was detected in ponies in the present study and no correlation with baseline insulin, insulin concentrations 60 minutes after an OST, adiponectin, triglycerides, or ACTH concentrations could be established. There might be several explanations why results of our study did not support the hypotheses. Steroid hormones appear to have a major influence on I-lactate metabolism and free cortisol concentrations are increased in overweight and obese equids.³⁷ Administration of exogenous corticosteroids to cardiac surgery patients and healthy horses decreased insulin sensitivity and increased blood glucose and I-lactate concentrations.^{35,38} In the study involving human cardiac patients, increased blood I-lactate concentrations appeared to be dependent on the presence of hyperglycemia.³⁸ Although a positive relationship between blood glucose and I-lactate concentrations was identified and increases in both variables were timely associated in the study in horses, it could not be determined whether hyperglycemia was a prerequisite for the development of hyperlactatemia.³⁵

All ponies in our study were clinically healthy and hyperglycemia was not detected in any of the ponies. This suggests that any endocrine abnormalities were well compensated and not severe enough to result in clinical signs. There was, therefore, no or only a limited effect on blood glucose concentrations. This could explain why no correlations between endocrine measures and blood I-lactate concentrations were detected in our study if increased glucose concentrations are the link between the 2 measurements. A small but significant difference between glucose concentrations was noted in ponies with and without ID and when comparing the first and last quartile of ACTH and insulin t60 concentrations. Investigating blood I-lactate concentrations in clinically symptomatic animals with more advanced endocrine disease such as PPID or equine metabolic syndrome might

therefore reveal different results. However, research in people suggests that not hyperglycemia but hyperinsulinemia and early metabolic changes on a cellular level are responsible for increasing I-lactate concentrations even before clinical signs develop.⁷

In our study, a single ACTH concentration was used to classify animals as having or not having increased autumnal ACTH concentrations using a previously established seasonal cutoff point from a study that used the same methodology.³⁰ While this approach is commonly used in daily equine practice,³¹ use of a dynamic test to classify animals might have provided a more standardized approach.³⁹ It is also possible that the study was underpowered to detect subtle differences in I-lactate concentrations. Although subject numbers were similar in studies in people,⁴⁰⁻⁴² most of these studies preselected the study subjects based on a known body mass and endocrine status. In the current study, clinically healthy ponies with no history of laminitis were selected without preselecting animals for body condition or prior knowledge of their endocrine status. It is possible that inclusion of more subjects or preselecting animals based on presence or absence of obesity or endocrine disease would have shown different results. It should also be acknowledged that measures of endocrine health were only investigated in ponies in our study and it is possible that findings in horses are different. However, based on this study it seems unlikely that I-lactate concentrations are a useful marker for detection of early or developing abnormalities. Only baseline I-lactate concentrations were determined in our study but in contrast to people, no differences in concentrations were found between ponies with and without ID. Differences in glucose and insulin metabolism are frequently not noticeable in a resting state but only become obvious after dynamic response testing.^{15,16} It is possible that continued measurements of I-lactate concentrations during dynamic testing would have identified increasing concentrations in ponies with ID.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Approved by Clinical Research Ethics Board of the Royal Veterinary College.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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