# Clinical insights: Advances in equine endocrinology

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*Introduction*

Over the last 25 years, understanding of equine endocrinopathies has improved dramatically. Developments include a better understanding of the pathophysiology of equine insulin dysregulation (ID) and the role it plays in endocrinopathic laminitis and refinement of antemortem tests for the diagnosis of both pituitary pars intermedia dysfunction (PPID) and ID. These developments are driven by the publication of peer-reviewed papers and the use of evidence-based medicine. This special collection of novel manuscripts and reviews (evidence and narrative) highlights Equine Veterinary Journal's contribution to this continuously developing field.

*Update on PPID*

PPID is a common progressive, age-related neurodegenerative disorder that affects horses and ponies of all breeds, as well as donkeys and mules with previous studies reporting a prevalence of 3% across the general equine population and 20% in animals ≥15 years of age (1, 2). This relatively high prevalence, especially in aged animals, reinforces the importance of the selection of PPID as the topic for development of British Equine Veterinary Association (BEVA) primary care clinical guidelines, which are included in this special collection. The goal of these guidelines is to provide evidence-based recommendations for the diagnosis and management of PPID directed at equine practitioners in an ambulatory setting. The panel utilized a previously established framework to identify clinical questions relevant to PPID, and to make recommendations related to those questions based on appraisal of the currently available literature (3, 4).

Hypertrichosis and altered/delayed hair coat shedding have long been described as an extremely common, almost pathognomonic, clinical sign of PPID in equids (5, 6). That assessment is supported by the evidence review conducted by Menzies-Gow and colleagues, which found evidence for a high clinical suspicion of PPID in animals with haircoat changes and stressed the importance of considering both animal age and clinical signs in case selection for PPID testing. The authors also discussed evidence that clinical signs such as hyperhidrosis, regional adiposity, epaxial muscle atrophy, laminitis, weight loss, recurrent infections or delayed healing, behaviour changes, or polyuria and polydipsia may prompt moderate suspicion of PPID, unless seen in animals < 10 years of age in which the prevalence of PPID is extremely low. Colbath *et al.* explored an infrequently described clinical finding in aged horses with advanced PPID, namely pathological fractures (7-10). To assess potential contributions of age or PPID to fracture risk, the study examined bone mineral density and biomechanical testing in weight-bearing (metacarpal/metatarsal) and non-weight bearing (vertebral) bones in equids with PPID and in both aged and young controls. Vertebral bone mineral density was decreased by up to 30% in equids with PPID compared to both aged and young controls; this finding was not apparent in weight-bearing (third metacarpal/metatarsal) bones, nor was it explained by significant variations in serum concentrations of ionized calcium or calcium-regulating hormones between PPID and control animals. Given the limited number of horses in this study, further investigations into the consistency of this finding across larger groups of equids with PPID, and into mechanisms by which increased ACTH and related peptides might impact bone density and strength, are needed.

Ideal diagnostic approaches for PPID have generated controversy for quite some time, with many studies generating conflicting results (11). In this collection, Menzies-Gow and colleagues found support for the currently recommended diagnostic approaches of assessment of basal plasma ACTH concentrations or ACTH responses to exogenous thyrotropin-releasing hormone (TRH) administration. Their evidence review demonstrated that these tests have good to excellent diagnostic accuracy depending on the pre-test probability of disease, which increases with increasing age and clinical signs described above. However, there is also substantial evidence that many factors – particularly breed

and season, but also geographic location, coat colour, diet, illness, and recent transport – impact test results and thus must be considered for accurate interpretation.

Two studies in this collection specifically focused on refining these currently utilized testing approaches. Drozdewska *et al.* investigated the effects of fasting and hay or hay/oat feeding on both basal and post-TRH ACTH concentrations in healthy equids. There were no differences in any test results among animals that were fasted overnight compared to those that had *ad libitum* access to hay, with or without a grain meal given 2 hours before testing. These findings corroborate previous similar investigations into effects of other feeding paradigms on PPID diagnostic testing (12, 13). Previous work has shown that imprecise sampling time substantially impacts TRH stimulation test interpretation for the 10-minute post-TRH time point (14). Bertin *et al.* assessed the clinical implications of imprecise sampling time on both 10- and 30-minute post-TRH sampling time points and found a similar impact of sampling precision for both protocols, further stressing the importance of exact timing when these samples are collected.

Lastly, the evidence appraised by Menzies-Gow and colleagues in the evidence review provides further support for the use of pergolide as a safe and effective therapy for PPID and reinforces that treatment with pergolide alone is not inferior to combination treatment with pergolide and cyproheptadine. The authors detail evidence that pergolide improves both clinical signs and endocrinologic testing in most treated animals, though insulin responses are not typically affected, and ACTH (basal or TRH-stimulated) concentrations may not decrease to non-PPID levels.

*Update on Obesity*

In this collection, two studies focused on equine obesity. Obesity has been reported to be prevalent in many pony breeds and Al-Ansari *et al.* reported similar finding for Connemara ponies in Ireland. Evidence of both regional and generalised obesity was reported in nearly 30% ponies, with the

incidence of laminitis, or a history of laminitis being just under 50% in this specific population. The assessment of obesity is almost always undertaken with subjective measures, such as condition scoring systems. An important addition to the field practitioner's approach to assessing obesity is provided in this collection. Bailey *et al.* describe an alternative method for estimating adiposity, based on a set of morphometric measurements. The body condition index correlated with both the percent body fat and with adiposity scores, suggesting that it is a reasonably accurate reflection of these other measurement techniques. However, the index was not as accurate at the extremes of body condition and was impacted by body shape, reducing its applicability to certain breeds.

*Update on ID*

Understanding of the complex interactions between the gastrointestinal tract (GIT) and the endocrine system in horses is improving rapidly. Several peptides produced by the GIT, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), can stimulate pancreatic release of insulin and dysregulation of these systems results in ID in horses. However, the role of GLP-2, which is co-secreted with GLP-1, is less well described. GLP-2 has intestinotrophic properties which result in an increased surface area for intestinal glucose uptake and an increase in the number of glucose transporters. The associated enhanced glucose uptake from feed could contribute to the development of hyperinsulinaemia in ID. In this collection, Sibthorpe *et al.* determined that the principal stimulus for equine intestinal GLP-2 secretion appears to be the arrival of nutrients in the gastrointestinal tract as GLP-2 concentrations in the ponies showed a 3- to 4-fold increase and peaked 4–6 h after eating, with trough concentrations occurring during the fasted state. Although an increase in plasma GLP-2 concentrations was observed after synthetic GLP-2 treatment, this effect was neither large nor sustained, nor was it greater than the effect of consumption of a forage-based meal and there was no effect on insulin secretion in response to eating. Thus, further studies are required to further elucidate the role of GLP-2 in equine ID. GLP-1 is secreted by enteral L cells after cleavage of

proglucagon, which is coded by the GCG gene. Active GLP-1 (aGLP-1) is a cleavage product shown to contribute to equine hyperinsulinaemia in some studies and its role in equine ID needs to be better defined. Sequence variations in the GCG gene are uncommon in mammalian species and minor genetic variations could have substantial downstream effects on the function of GCG and its incretin products. Given that GLP-1 secretion has been shown to differ between healthy horses and those with ID, it is feasible that this effect could be underpinned by a difference in the coding region of the GCG gene. Fitzgerald *et al.* demonstrated that both the large and small intestines are sites of equine GLP-1 secretion; however, despite differences in postprandial aGLP-1 concentrations between horses with and without ID, the GCG gene sequence of the exons was 100% identical. Thus, these differences are not a consequence of genetic differences.

A recent area of research focus has been on the role of adipose tissue-derived cytokines (adipokines) in metabolic and endocrine disease including the potential importance of adiponectin to equine endocrinopathies. This collection includes two studies by Barnabé *et al.* that used a cohort of native-breed ponies to examine relationships between total adiponectin concentration and aspects of the pathophysiology of ID and obesity. Total adiponectin was not as strongly correlated with body condition, body shape and breed as expected and inducing short-term ID did not alter total adiponectin concentrations. Critically, the two manuscripts from this team indicate that we are far from understanding the role that adiponectin plays in equine obesity and ID, and further study on the relationship between total adiponectin and insulin regulation, in both health and disease, is required.

In this collection, two studies examined factors that might affect the insulin response to an oral sugar test, which is used as part of the diagnostic approach to ID. A UK cohort study of native-breed ponies by Knowles *et al.* found that the insulin response to oral sugar was associated with multiple variables, notably signalment, obesity and some biochemical markers (ACTH and total adiponectin). However, he insulin response could not be predicted from the physical appearance of the individual animal. In a smaller study of Shetland and Welsh pony breeds in Australia, Clark *et al.* reported similar findings with

age, being of female sex and owner-reported obesity all associated with insulin responses to the oral sugar test.

Insulin and adiponectin are commonly measured in clinical practice to detect ID and hypoadiponectinaemia (an additional feature of equine metabolic syndrome [EMS]). Currently, both hormones are measured in serum/plasma, but saliva is an attractive alternative as it can be collected more conveniently and has proved useful for the measurement of these hormones in other species. Additionally, equine saliva is used to measure other metabolic hormones such as cortisol and antibodies indicating tapeworm burden. In this collection, Barnabé *et al.* demonstrated that insulin was measurable in equine saliva with low inter- and intra-assay variability using one of the automated assays currently available in the UK and the process of saliva collection was not associated with stress. Unfortunately, salivary and serum insulin concentrations were not significantly correlated, and adiponectin was not detectable in saliva. Thus, saliva is not a viable alternative to blood currently.

The mainstays of treatment for equine ID have not changed greatly despite the surge in research aiming to improve understanding of the epidemiology and pathophysiology of the condition. Alteration of the diet to reduce non-structural carbohydrate content coupled with an increase in the duration and intensity of exercise is considered the best strategy. However, this approach in only successful in some animals; thus, there is a need for an efficacious pharmaceutical treatment option. Metformin has been associated with inconsistent outcomes when used in the treatment of equine ID and seems very sensitive to the dose, formulation and dosing schedule used. In this collection, Colmer *et al.* examined the short-term effect of metformin (dosed at 30 mg/kg) on the insulin response to an oral sugar test (OST) and found no reduction in the insulin response regardless of whether it was dosed orally 1h, 2h or 6h prior to the OST. This outcome adds weight to the bank of evidence that fails to support metformin as an efficacious pharmaceutical option for treating ID, at least for the dose and formulation tested.

*Update on use of corticosteroids in animals with ID*

Corticosteroids are frequently used in equine medicine for the treatment a wide range of conditions including osteoarthritis. Previously anecdotal evidence suggested that exogenous corticosteroid use was associated with an increased risk of laminitis with intra-articular injection of triamcinolone of particular concern. A review of the available scientific evidence suggested that there is currently no conclusive evidence to support a causal association between therapeutic systemic corticosteroid administration and the development of laminitis in healthy adult horses/ponies (15). However, there is weak evidence of an association between administration of multiple doses of systemic corticosteroid and the onset of laminitis in adult horses/ponies with underlying endocrine disorders or severe systemic disease (15). In this collection, Boger *at al.* determined the effect of intraarticular triamcinolone injection on blood insulin and glucose concentrations in healthy insulin-sensitive horses. Blood insulin and glucose concentrations were increased for 48 hours following injection; however, the average peak insulin concentration was <45μIU/mL, a concentration considered in the normal range for horses undergoing an oral sugar test. Thus, intraarticular triamcinolone does not result in circulating insulin concentrations likely to induce laminitis in insulin-sensitive animals, but further work is needed determine the effect in animals with ID.

*Update on thyroid disorders*

In some countries, blood thyroid hormone concentrations are routinely measured in horses and hypothyroidism is a common diagnosis. However, while benign thyroid tumours are common in older horses, other disorders like primary hypothyroidism or hyperthyroidism in adult horses and congenital hypothyroidism in foals are rare. There is a common misunderstanding regarding hypothyroidism in adult horses, especially when associated with the clinical profile of obesity, lethargy, and poor performance as these signs accompany hypothyroidism in dogs and humans. Additionally, low blood thyroid hormone concentrations are often detected in horses as a secondary response to metabolic

and disease states. Thus, hypothyroidism is commonly misdiagnosed. In this collection, the review by Bertin *et al.* focuses on thyroid gland pathophysiology in adult horses and foals, interpretation of blood thyroid hormone concentrations, and evaluation of horses with thyroid disorders. It also discusses the use of T4 supplementation in equine practice. Assessing equine thyroid function involves measuring thyroid hormone concentrations, including total and free fractions of thyroxine (T4) and triiodothyronine (T3); however, interpreting these results can be challenging due to the pulsatile secretion of thyroid hormones and the many factors that can affect their concentrations. Instead, dynamic testing, such as the TRH stimulation test, is essential for confirming hypothyroidism. Although not associated with true hypothyroidism, thyroid hormone supplementation is commonly used in equine clinical practice to help manage obesity, particularly in animals with concurrent ID, and poor performance. The rationale for the former use is that it speeds up the metabolic rate and so increases the rate of calorie consumption. The latter use may be a consequence of detection of a low T4 concentration on a screening panel or due to perceived poor performance. However, levothyroxine supplementation is not recommended for the treatment of equine poor performance due to a negative effect on cardiac function and an increased risk of adverse effects such as cardiac arrhythmias.

References


1. McGowan TW, Pinchbeck GP, McGowan CM. Prevalence, risk factors and clinical signs predictive for equine pituitary pars intermedia dysfunction in aged horses. Equine Vet J. 2013;45(1):74-9.
2. Ireland JL, McGowan CM. Epidemiology of pituitary pars intermedia dysfunction: A systematic literature review of clinical presentation, disease prevalence and risk factors. Vet J. 2018;235:22-33.
3. Bowen IM, Redpath A, Dugdale A, Burford JH, Lloyd D, Watson T, et al. BEVA primary care clinical guidelines: Analgesia. Equine Vet J. 2020;52(1):13-27.
4. Freeman SL, Ashton NM, Elce YA, Hammond A, Hollis AR, Quinn G. BEVA primary care clinical guidelines: Wound management in the horse. Equine Vet J. 2021;53(1):18-29.
5. Kirkwood NC, Hughes KJ, Stewart AJ. Prospective Case Series of Clinical Signs and Adrenocorticotrophin (ACTH) Concentrations in Seven Horses Transitioning to Pituitary Pars Intermedia Dysfunction (PPID). Vet Sci. 2022;9(10).
6. McFarlane D. Equine pituitary pars intermedia dysfunction. Vet Clin North Am Equine Pract. 2011;27(1):93-113.
7. Boujon CE, Bestetti GE, Meier HP, Straub R, Junker U, Rossi GL. Equine pituitary adenoma: a functional and morphological study. J Comp Pathol. 1993;109(2):163-78.
8. Loeb WF, Capen CC, Johnson LE. Adenomas of the pars intermedia associated with hyperglycemia and glycosuria in two horses. Cornell Vet. 1966;56(4):623-39.
9. King JM, Kavanaugh JF, Bentinck-Smith J. Diabetes mellitus with pituitary neoplasms in a horse and a dog. Cornell Vet. 1962;52:133-45.
10. van der Kolk JH, Kalsbeek HC, van Garderen E, Wensing T, Breukink HJ. Equine pituitary neoplasia: a clinical report of 21 cases (1990-1992). Vet Rec. 1993;133(24):594-7.
11. Meyer JC, Hunyadi LM, Ordonez-Mena JM. The accuracy of ACTH as a biomarker for pituitary pars intermedia dysfunction in horses: A systematic review and meta-analysis. Equine Vet J. 2022;54(3):457-66.
12. Diez de Castro E, Lopez I, Cortes B, Pineda C, Garfia B, Aguilera-Tejero E. Influence of feeding status, time of the day, and season on baseline adrenocorticotropic hormone and the response to thyrotropin releasing hormone-stimulation test in healthy horses. Domest Anim Endocrinol. 2014;48:77-83.
13. Restifo MM, Frank N, Hermida P, Sanchez-Londono A. Effects of withholding feed on thyrotropin-releasing hormone stimulation test results and effects of combined testing on oral sugar test and thyrotropin-releasing hormone stimulation test results in horses. Am J Vet Res. 2016;77(7):738-48.
14. Thane K, Uricchio C, Frank N. Effect of early or late blood sampling on thyrotropin releasing hormone stimulation test results in horses. J Vet Intern Med. 2022;36(2):770-7.
15. McGowan CM, Cooper D, Ireland JL. No evidence that therapeutic systemic corticosteroid administration is associated with laminitis in adult horses without underlying endocrine or severe systemic disease. Veterinary Evidence. 2016;1(1).