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A one-health lens offers new perspectives on the importance of endocrine disorders in the equine athlete

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ABSTRACT

Endocrine disorders are associated with joint pain and tendon injury in humans, but the effects in the horse are only starting to be understood. Similar patterns of clinical signs and injury appear to affect horses and humans for both orthopedic and endocrine disorders, supporting the use of a one-health approach to tackle these issues. In this Currents in One Health, we will discuss common equine endocrinopathies, current testing recommendations, dietary management, genetic predispositions, and endocrine disorders' effects on performance. Our aim is to use a one-health lens to describe current comparative research so that veterinarians can employ cutting-edge preventative, diagnostic, and therapeutic recommendations. Identified key gaps in knowledge include whether equine metabolic osteoarthritis exists, if steroid joint injections are safe in horses with endocrine disorders, and if the return to performance percentage improves with concurrent treatment of endocrine and musculoskeletal disorders. Key takeaways include that the relationship between endocrine disorders and musculoskeletal disease in the horse goes beyond laminitis to include lameness, muscle atrophy, suspensory ligament degeneration, osteochondritis dissecans, and potentially metabolic osteoarthritis. Approaches learned from human and equine comparative studies can offer insight into injury recognition and management, thus mitigating the impact of endocrine disorders on performance in both species. Readers interested in an in-depth description of current and future research involving pathophysiology, novel interventions, and multiomic approaches to identify individuals with athletic limitations induced by endocrine disorders are invited to read the companion Currents in One Health by Manfredi et al, *AJVR*, February 2023.

Endocrine Disorders: a One-Health Issue

Endocrine disorders and related obesity affect an increasing number of humans, horses, dogs, and cats, with negative impacts on multiple body systems.[1–3] Human metabolic syndrome (MetS) is a consortium of disorders, which is a major risk factor for development of diabetes and cardiovascular disease that affects 25% of the US population.[4,5] The average total yearly hospital costs of an individual with MetS is 1.6 times more than that of a healthy individual.[6] A sedentary lifestyle and obesity can predispose a human to developing MetS, and these are similar risk factors in animals.[7–9] To be diagnosed with MetS, humans must demonstrate central obesity and 2 of the following: reduced high-density lipoprotein cholesterol, elevated blood pressure, fasting blood glucose, and/or triglycerides.[7] Horses diagnosed with equine metabolic syndrome (EMS) also demonstrate marked inappropriate glucose/insulin dynamics (insulin dysregulation [ID]), dyslipidemia, obesity, and adiposity, similar to humans with MetS.[10–12] Humans on chronic steroids for treatment of chronic obstructive pulmonary disease (COPD) or autoimmune disease[13,14] experience cortisol dysregulation similar to horses with pituitary pars intermedia dysfunction (PPID), another common equine endocrine disorder.[15] Because endocrine disorders are commonly seen in clinical practice, veterinarians and human medical doctors are in a unique position to share information to improve health outcomes, embodying the idea of a one-health approach.

In terms of athletic performance, endocrine disorders have been associated with both bone and soft tissue pathologies in humans. Metabolic osteoarthritis, thought to be due to chronic low-grade systemic inflammation,[16–18] is now a recognized arthritis subtype associated with MetS in humans, for which there has been little research in horses. Tendon injury and rupture, specifically of the Achilles, has been documented in humans secondary to diabetes and chronic steroid administration for treatment of COPD or autoimmune disease.[13,14] The cortisol dysregulation present in those cases can mimic the pathophysiol-

ogy experienced in horses with PPID, and PPID has been linked to human Parkinson disease.[19–21] MetS in humans also has negative effects on healing tissues, with the proinflammatory state causing increased scarring leading to future tendon injury, which could also occur in horses.[22]

The similar clinical signs and shared pathophysiology behind orthopedic and endocrine disorders in humans and horses suggest that adopting a one-health approach can facilitate obtaining optimal health outcomes in both species. The purpose of this article is to review the common equine endocrinopathies, current testing recommendations, dietary management, genetic predispositions, and endocrine disorders' effect on performance **(Table 1)**, gaining insights from comparative human studies. Readers interested in an in-depth description of current and future research involving pathophysiology, novel biomarkers, and interventions for individuals with athletic limitations induced by endocrine disorders are invited to read the companion Currents in One Health by Manfredi et al, *AJVR*, February 2023.

Common Adult Equine Endocrine Disorders

PPID, EMS, and ID (which can be a feature of both PPID and EMS) are the main equine endocrine disorders affecting adult horses. PPID, a neurodegenerative age-associated disorder, occurs when there is a reduction in dopaminergic inhibition of pars intermedia melanotropes, giving rise to hyperplasia, microadenomas, and macroadenomas. Clinical signs vary depending on the stage of disease but commonly include the following: hypertrichosis, delayed shedding, loss of topline musculature, abnormal sweating, polyuria and polydipsia, chronic infections, and chronic laminitis **(Figure 1)**. Treatment most often includes administration of pergolide mesylate, a dopamine receptor agonist, which is a prohibited substance according to the Fédération Équestre Internationale but allowed under a therapeutic use exemption by the US Equestrian Federation.[23–26] Twenty percent of horses over 15 years of age and 30% of horses older than 30 years of age have some degree of PPID.[26] ID, defined as abnormalities in insulin metabolism leading to resting hyperinsulinemia, postprandial hyperinsulinemia, or tissue insulin resistance, can also be present in cases of PPID, which can subsequently lead to laminitis. Horses with both PPID and EMS are known to have higher basal insulin concentrations and be more severely affected.[27]

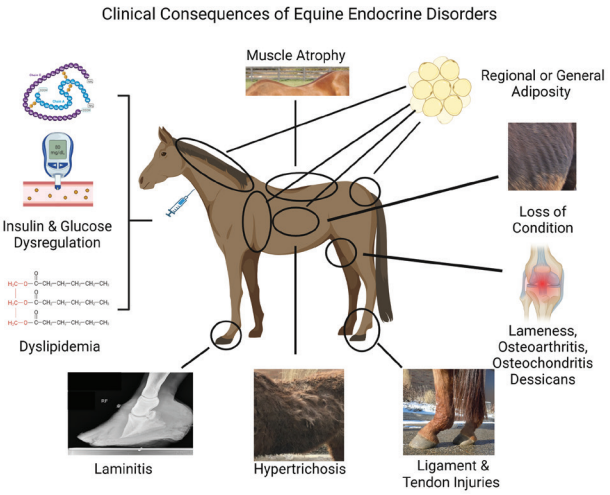

Figure 1—Clinical consequences of equine endocrine disorders. Created with BioRender.com.

EMS is characterized by regional or generalized adiposity, ID, a predisposition to laminitis, and lipid dysregulation (Figure 1). These abnormalities are most often treated with diet and exercise modifications.[10–12] EMS has been traditionally associated with either tissue-level insulin resistance (IR) or postprandial hyperinsulinemia, with both of those falling into the category of horses with ID. This term encompasses abnormal fasting hyperinsulinemia, excessive insulin response to oral or IV sugar administration, as well as evidence of IR.[12,28–30] This definition reflects the idea that hyperinsulinemia can occur independently of IR and is not just a sequela of IR. Historically, IR has been associated with metabolic syndrome in humans and horses.[10,11,31] The presence of IR is an important pathophysiologic component of EMS,[10,11,32,33] as evidenced by the reported clinical association between the hyperinsulinemia in insulin-resistant animals and incident laminitis, as well as the experimental induction of laminitis following 48 hours of euglycemic-hyperinsulinemia in previously normal horses.[34,35] MetS poses a shared health issue with horses and humans in that environmental contamination with endocrine-disrupting chemicals is associated with development of MetS in both species.[36,37]

While hypothyroidism is often diagnosed in the horse, it is uncommonly a cause of clinical signs.[38,39] Horses with PPID have been documented to have lower serum free thyroxine concentrations than age-matched controls, which is postulated to occur

Table 1—Equine performance issues and the endocrine-related conditions associated with them.

Equine performance and/or musculoskeletal issues	Endocrine association
Endocrinopathic laminitis	Insulin dysregulation associated with EMS and PPID[27,35,112,113,149–153]
Suspensory ligament desmitis/degeneration	PPID[119,120,154,155]
Muscle atrophy and possible secondary back pain	PPID[24,26,75,126]
Obesity and lameness, exercise intolerance	Obesity, EMS [10,12,65,106,108,134,156]
Osteochondritis dissecans	EMS[143]
Systemic inflammation, which can support a metabolic osteoarthritis phenotype	EMS, obesity[130,157–159]
Cardiac arrhythmia	Treatment of hypothyroidism with levothyroxine[43]

due to suppression from high circulating levels of glucocorticoids, the clinical significance of which is unknown.[39] In humans, hypothyroidism is more clinically significant but only has a weak link to MetS in men.[40] Of note for equine and human athletes, treatment with levothyroxine for purported low thyroid levels has been associated with increased incidence of arrhythmias, both in humans[41,42] and horses.[43]

Current Testing Recommendations for Equine Endocrine Disorders

Testing for PPID

Detection of excessive endogenous plasma ACTH derived from the abnormal pars intermedia is the most common diagnostic test for PPID. Collection of a static baseline blood sample or dynamic testing with a thyrotropin-releasing hormone (TRH) stimulation test may be performed **(Figure 2)**. The TRH stimulation test is the most accurate for diagnosis unless it is performed in the fall when it is less repeatable.[44–46] The TRH stimulation test involves collection of a baseline blood sample (plasma sample in an EDTA tube), administration of 0.5 mg (equids < 250 kg) or 1 mg (equids > 250 kg) of TRH IV, and collection of a second blood sample (EDTA plasma) exactly 10 minutes after TRH administration. The 10-minute timing is critical, as collection of blood 1 minute earlier or later resulted in a different interpretation of the results in 21% of horses.[47] This test must be performed before assessing for ID with an oral sugar test (OST).[44] Biochemical measurements should be interpreted in conjunction with the horse's history and clinical signs. A baseline ACTH measurement > 40 pg/mL (December to June), > 50 pg/mL (July and November), > 75 pg/mL (August), or > 90 pg/mL (September to October) adds support for a diagnosis of PPID. Following administration of TRH, an ACTH measurement > 200 pg/mL (January to June) adds support for a diagnosis of PPID.[48,49] From July to December, current diagnostic cutoffs are not published due to a high number of false positives, but some endocrinology laboratories have their own thresholds. The TRH stimulation test should be used to identify negative cases during this time, with an ACTH measurement < 100 pg/mL decreasing the likelihood for a diagnosis of PPID.

Testing for equine metabolic syndrome and insulin dysregulation

Current recommended clinical tests for EMS and ID include the OST (Figure 2) and the insulin tolerance test.[50] Previous static testing of fasting insulin (positive if insulin concentrations were > 20 µU/mL) has been demonstrated to have poor sensitivity but good specificity, with the test misidentifying a truly affected animal up to 85% of the time.[51] The OST for EMS/ID was initially performed with a lower dose of corn syrup (0.15 mL/kg, PO; Karo Syrup Light; ACH Food Companies Inc).[44,52] A recent report[53] evaluating

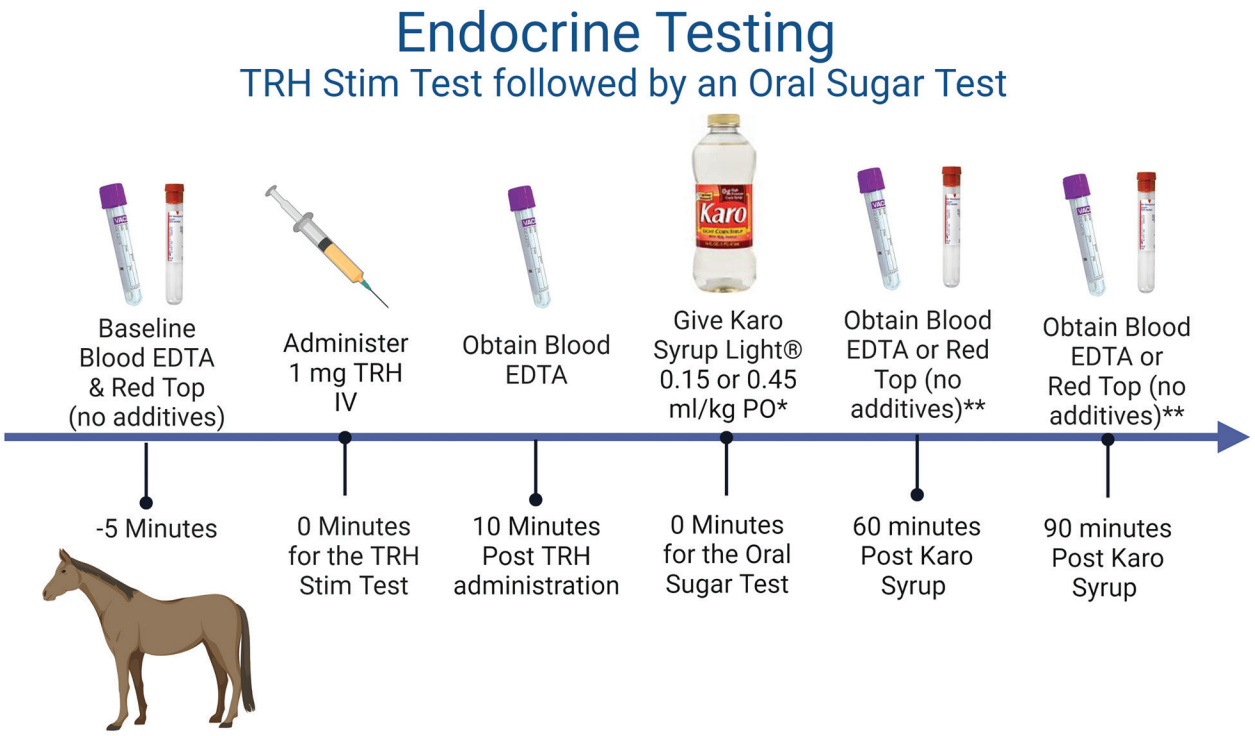

Figure 2—Timeline for sequential endocrine testing. A thyrotropin-releasing hormone (TRH) stimulation (Stim) test to assess for equine pituitary pars intermedia dysfunction followed by an oral sugar test to assess for insulin dysregulation. *Dose of corn syrup is either 0.15 or 0.45 mL/kg, PO. **Blood tube used is laboratory dependent. Created with BioRender.com.

ponies advocated for dosing with a higher amount of corn syrup (0.45 mL/kg, PO) to improve sensitivity, but further research in horses should be performed to evaluate the need for this dose. Horses should be fasted 3 to 12 hours before the test.[54] Blood should be pulled for insulin evaluation at 60 and 90 minutes postadministration of corn syrup (red top [no additives] or EDTA, depending on the laboratory to be used for insulin analysis). A horse demonstrates ID if insulin is > 45 µU/mL at the lower dose and > 62 µU/mL (Immulite2000; Siemens Medical Solutions USA Inc) or > 65 µU/mL (radioimmunoassay) at the higher dose.[55] Previously, insulin could not be assessed stall side, but a new device (Wellness Ready; Wellness Ready Labs) suggests that it can be used in the field, detecting insulin concentrations from 20 to 99.9 µU/mL. Company-reported sensitivities and specificities range from 87% to 96%, but peer-reviewed published reports are not available currently.[56]

The insulin tolerance test is performed in an unfasted state, and blood glucose concentrations are analyzed at 0 and 30 minutes after IV administration of regular insulin (0.10 IU/kg).[54] A horse should be fed after the second blood sample is obtained. A horse is positive for IR if the glucose concentration is not decreased by > 50% in 30 minutes.[50] This test can be performed stall side but doesn't assess the enteroinsular axis, which we know is important in the pathophysiology of EMS.[29]

Human tests for metabolic syndrome have used static tests for glucose, changes in glucose in response to sugary drinks (in humans glucose is more indicative of the presence of MetS than insulin), A1C, low levels of high-density lipoprotein cholesterol (< 40 mg/dL), triglycerides (> 150 mg/dL), and arginine stimulation tests.[57,58] Of these, triglycerides have been considered for use in the horse (with values > 57 and 94 mg/dL being described as thresholds).[59,60] Adult horses have an insulin response to arginine,[61] as do pony foals that were found to be insulin resistant at 1 day of age,[62] and these could be explored as future tests. Further details about recommended diagnostic tests for endocrine disorders can be found at the Equine Endocrinology Group.[63]

Genetic Predispositions to Equine Endocrine Disorders that Could Affect Performance

Metabolic syndrome is a complex genetic disorder, indicating that both the environment and genetics contribute to its pathophysiology, predisposing specific groups to developing IR/ID. While women appear predisposed to MetS, particularly after menopause, there do not appear to be sex differences in predisposition to endocrine disorders in our equine athletes.[27,64] Admittedly most of the research performed has been in intact mares and geldings, so data for spayed mares and stallions are lacking.

In horses, Arabians, Tennessee Walking Horses, Andalusians, Morgans, and ponies are among those breeds considered to be at high risk for EMS, and genetic investigations have been focused on several of these breeds.[10,65,66] In Welsh ponies and Morgan horses, 8 EMS traits were found to be moderately to highly heritable, indicating that genetics is significantly contributing to EMS.[67] Genome-wide association analyses narrow down specific regions of the genome harboring risk alleles and have identified hundreds of regions of the genome contributing to EMS. In a population of Morgan horses and Welsh ponies, 142 and 266 candidate regions were identified, respectively, of which 65 of these regions were shared between both breeds.[68] Four unique candidate regions were associated with alterations in metabolomics in Arabian horses with EMS.[69] Two EMS genetic variants have been proposed, including a pony-specific nonsense mutation in *HMGA2* in Welsh ponies[70] and a polymorphic guanine homopolymer in the 3′ untranslated region of *FAM174A* in Arabian horses.[71] Notably, the association with EMS and the *FAM174A* variant was not replicated in 2 independent studies including a cohort of ponies[72] and Arabians and other large-breed horses.[73] These data support that EMS is the result of both unique and shared genetic risk alleles between horse breed, which is analogous to what has been found in humans with MetS with variability in heritability estimates and associated quantitative trait locus among ethnic groups.[74] This also indicates that a genetic test for EMS would require a well-validated panel of genetic variants to accurately assess a horse's genetic risk.

Breed predilection for PPID in Morgan horses and ponies has also led to the hypothesis that PPID has a genetic component.[75] This is further supported by similarities in the underlying pathogenesis of PPID and Parkinson disease, a human disease also caused by dopaminergic neurodegeneration in aged individuals. Parkinson disease is considered a moderately heritable disease, and genetic evaluation has led to the identification of 30% of the genetic variants leading to familial Parkinson disease and 3% to 5% of the sporadic form.[76–80] Although the heritability and specific genetic variants of PPID have not been identified, several studies have identified alterations in genetic expression between PPID cases and controls, bringing valuable insight into the underlying pathophysiology of PPID. In skeletal muscle, overexpression of m-calpains in cases could explain the significant muscle atrophy common in horses with PPID.[20] Further, upregulation of proopiomelanocortin, PC1, and PC2 messenger RNA in the pituitary gland of PPID cases, without concurrent changes in the proopiomelanocortin protein or amino acid levels, suggests that the lack of ACTH bioactivity in horses with PPID is due to a posttranslational modification or secondary defect, which requires further exploration.[19]

Therefore, the genetic variants of equine endocrine disorders are still in the discovery phase, but the knowledge of increased genetic risk should still be used to make strategic breeding decisions. Lines that have a heavy prevalence of EMS or PPID, or individual horses that show clinical signs at an earlier age, should be bred with lower prevalence lines or horses that have not shown clinical signs of disease to reduce the overall

genetic risk in their offspring, limiting the risk of developing laminitis and other endocrine-associated musculoskeletal conditions. Further, the breeding value of individual horses that show severe clinical signs of disease should be seriously considered. Notably, given that complex genetic disease is the result of dozens to hundreds of genetic alleles, the goal should not be to eliminate the disease from the population but to reduce the overall genetic risk in future generations.

Current Nutritional Recommendations for Equines with Endocrine Disorders to Maximize Performance

Diet is a major concern in the management of EMS patients and other animals with evidence of ID (eg, older horses with or without PPID) to maintain optimal performance. In animals kept at pasture, hyperinsulinemic laminitis often coincides with an increase in forage nonstructural carbohydrate (starch plus a water-soluble carbohydrate) content and exacerbation of hyperinsulinemia. In addition, the feeding of a starch-rich diet results in a decrease in insulin sensitivity when compared to a low-starch diet that contains higher fat (oil) and/or fiber content.[81–85] Horses survive primarily on high-roughage diets with varying amounts of protein, fat, and fiber; however, these roughage diets are often supplemented with a grain concentrate to meet the animal's daily energy demand. The glycemic index, influenced by the type of carbohydrate, of a feed characterizes the postprandial glycemic response to a measured amount of feed.[86] Hay is often classified as having a low glycemic index while grains have a high glycemic index. Starch and sugar concentrates have a higher glycemic index compared to primarily fat and fiber concentrates.[87] Several studies have linked nutrition,[60,88] forage nonstructural carbohydrate content,[89] lack of physical activity,[90,91] endocrine-disrupting chemicals,[36] and alterations in the gut microbiome[92] to ID, obesity, and/or laminitis. Dietary recommendations for horses at risk for hyperinsulinemia-associated laminitis are aimed at reducing the postprandial insulin response and improving insulin sensitivity. PPID specific diets have not been determined, but protein and calcium concentrations higher than that recommended for healthy aged horses may be desirable.

The ability to meet a horse's maintenance energy requirements allows the animal to sustain fundamental physiologic processes to optimize performance. An animal's energy requirements change due to a number of factors such as life stage, climate, exercise (performance) level, and breed. When an animal's energy intake exceeds energy requirements, a positive energy balance occurs, leading to weight gain. Dietary modification for horses with ID should focus on nonstructural carbohydrate content reduction and caloric reduction (if obese). It is recommended that the nonstructural carbohydrate content of the diet be < 10% (dry-matter basis) to improve insulin and glucose dynamics.[81,85,93,94] A forage analysis can be a valuable tool when evaluating and designing a nutrition regimen for the equine athlete, as the nonstructural carbohydrate content of pasture and hay, the forages most commonly consumed by horses, are variable. If the addition of a concentrate is needed to meet daily energy requirements, a low-starch/low-sugar feed that induces a low glycemic response should be selected. Alternatively, a horse that can be maintained on a forage-only diet may benefit from consumption of a ration balancer to provide the adequate balance of amino acids, vitamins, and minerals. Some caution should be taken with ration balancers that have higher protein, as those have been shown to induce a more pronounced insulin response, albeit not as dramatic as that of higher nonstructural carbohydrate feeds.[95,96] Additionally, if grain is fed, stationary objects placed below the feed are most effective at slowing down the time it takes horses to eat food, which may blunt the postprandial insulin and glucose peaks.[97] Caloric restriction should be undertaken in overconditioned or obese horses to induce weight loss. The daily caloric intake in these horses should be 1.5% to 2.0% of body weight in low nonstructural carbohydrate forage. Caloric restriction to 1.0% to 1.5% of body weight in forage may be necessary in some horses.[98,99] This approach should only be utilized until a suitable body condition score is accomplished. The use of a grazing muzzle limits the forage consumption rate in horses that cannot be removed from pasture.[100,101] Other strategies to alter postprandial insulin dynamics include feeding multiple small meals throughout the day and lengthening the meal consumption time.[102,103]

In addition to dietary modifications, low-intensity exercise, if the horse's condition permits, improves insulin dynamics.[104,105] Diet or exercise proved to be efficacious at improving weight, body condition score, and neck circumference variables, but only the latter improved neck circumference-to-height ratio.[105] Exercise in the face of a high-starch diet was found to keep insulin sensitivity levels similar to animals on a high-fat diet.[82]

Equine Endocrine Disorders and Performance

Hyperinsulinemia-associated laminitis

When thinking about endocrine disorders that affect performance, laminitis is most often described.[106] Endocrine disorders are the top cause of laminitis in the horse, with underlying ID (and resultant hyperinsulinemia) thought to be the driver of this pathology.[12,107,108] Laminitis secondary to high insulin concentrations can be sequelae of either EMS or PPID, with horses that suffer from both being more likely to have a more severe lameness.[27] A USDA survey found that 13% of farms surveyed had at least 1 case of laminitis in the past year, with laminitis representing 7.5% to 15.7% of the reported lameness cases.[109,110] Over half of the laminitis cases in that study were predicted to be preventable if measures to prevent endocrinopathic laminitis development had been taken. While only 4.7% of horses with laminitis were euthanized and 73.7% returned to their

former use, the level of athleticism of that cohort is unknown.[110] An older study[111] out of the UK found a 77% return to athletic soundness postlaminitis of any cause, with a worse prognosis for cases in which the coffin bone had sunk. As the majority of cases in that study were ponies, the rigors of their athletic pursuits were not clear.[111] Of increasing concern is that the recurrence rate of hyperinsulinemia-associated laminitis was found to be 34.1% within 2 years, with high basal insulin levels and higher Obel scores increasing risk.[112] Additionally, owners are apt to miss clinical signs of laminitis, which can delay treatment and affect prognosis.[113] The effects of laminitis can certainly be career disrupting or ending in the case of our equine athletes, and the full extent of its impact over the lifetime of horses competing in different disciplines is not currently known.

Pituitary pars intermedia dysfunction and tendon and ligament injury

Endocrine disorders are associated with joint pain and tendon injury in humans,[17,114–118] and preliminary investigations in horses with PPID have shown a greater percentage of soft tissue injuries, particularly of the suspensory.[119,120] In humans, the chronic excessive circulation of glucocorticoids, commonly secondary to oral steroid treatments for COPD or autoimmune disease, can result in similar clinical signs to PPID in horses such as muscle wasting and hypertrichosis. Steroids block production of collagen and tenocyte expansion, and acute Achilles tendon rupture has been reported in humans secondary to high endogenous or exogenous levels of circulating glucocorticoids or type 2 diabetes.[13,14,114,116,117,121] In horses, the suspensory ligament was noted to be the site of greatest soft tissue injury in equine athletes overall (approx 14%), with dressage horses experiencing injury in this region > 25% of the time.[122] In addition, the suspensory ligaments of horses with PPID had a higher histology score,[119] indicating more degeneration than age-matched controls. Other work suggests that PPID may be associated with systemic proteoglycan accumulation, as changes have been found in multiple other tissues and ligaments (sclerae, cardiovascular tissues, and patellar ligaments).[119,120] An increase in suspensory injury in sport horses > 10 years of age showing clinical signs of PPID (representing 70% of lame horses) was also noted, with 16% of the cohort demonstrating ID as well.[123] This raises the question of whether high levels of circulating insulin in horses can contribute to other lameness causes as suggested by some studies of humans.[16,17,118]

Muscle wasting along the topline in horses with PPID can be an issue with saddle fit and related back pain. In 1 field study, 74% of horses with back pain were deemed lame and back problems were diagnosed in 32% of lame horses.[124,125] Another study concluded that peak pressure values at the trot under the saddle > 3.1 N/cm^2 (31 kPa) were correlated with back pain,[125] and unpublished work from 1 author (JMM) has demonstrated peak whole pad saddle pressures of 40 kPa on landing from 1-m jumps. Since muscular support for saddle placement is key, there is reasonable concern that muscle wasting can contribute to overloading of the bony and ligamentous structures in the back leading to pain. Interestingly, treatment of PPID in horses with pergolide was not found to improve muscle mass,[126] suggesting that other additional rehabilitation measures, such as dynamic mobilization exercises, are needed to regain muscle mass.[127] Muscle atrophy can additionally contribute to destabilization of joints, which can worsen conditions such as osteoarthritis.[128]

Equine metabolic syndrome, lameness, obesity, osteoarthritis, and osteochondritis dissecans

EMS and lameness concerns affect a large percentage of our horse population. An estimated 20% to 40% of the equine population is at risk for the development of EMS/ID.[108] In 1 Canadian province and in the UK, over 30% of horses are overweight or obese, and obesity is a prominent component of EMS/ID.[2,129] Obesity has been linked to equine systemic levels of inflammation,[130] and although obesity itself doesn't guarantee each horse has ID, it is a common feature.[12,61,131] Lameness is a very common issue on horse farms, and a USDA study[110] revealed that 36% to 79% of farms surveyed had a case of lameness over the past year, with approximately 50% of cases being related to leg or joint issues, often due to arthritis or other degenerative joint diseases. This accounted for approximately 468,000 horses affected by lameness per year,[110,132] with total costs of losses due to lameness nationally reaching $678 million and an average of 110 days lost per lameness event.

One contributor to lameness and exercise intolerance that has links to endocrine disorders is obesity, which is becoming more prevalent in the general horse population.[131] An increased body weight is thought to contribute to exercise intolerance and exacerbate lameness.[133,134] For 1 example, at a 160-km endurance race, heavier horses more often did not complete the race due to increased lameness issues.[134] Metabolic disease is associated with joint pain in humans.[17,114–118,135] It is not clear whether ID plays a role in lameness, but the fact that resveratrol-based nutritional supplements in horses have been shown to both decrease lameness and improve insulin dynamics could suggest a link.[136,137] Metabolic osteoarthritis has been documented in humans as a subtype of osteoarthritis that could also be occurring in our equine patients, and future work should investigate its occurrence.[16,17,118]

In humans with diabetes, IA administration of glucocorticoids has caused issues with glucose and insulin regulation due to their systemic absorption, which results in substantially raised blood glucose levels.[138,139] It is unknown whether the same happens in horses post IA injection for treatment of OA, but systemic steroids can alter glucose metabolism[140] and controversially they have been linked to laminitis bouts.[141] As IA steroid injections to treat equine joint disease are commonly performed, the finding that administration of glucocorticoid therapy within

the past 30 days increased the odds of developing laminitis is of true concern.[142] Prospective studies evaluating blood insulin and glucose levels post IA injection of steroids are warranted. Until that time, alternative regenerative medicine therapies and physical rehabilitation strategies may be selected for cases in which horses are deemed at risk for laminitis whether due to signalment, diet, or currently diagnosed endocrine conditions. Studies evaluating regenerative medicine IA therapies in horses can also lead the way to these becoming available for humans with diabetes. In this sense, collaborative efforts between the human and veterinary medical communities can facilitate assessment and possible adoption of novel therapies, a benefit attainable due to the one-health approach.

Obesity and ID have been linked to developmental orthopedic disease in horses.[143–145] Studies evaluating osteochondritis dissecans (OCD) in young Standardbred or Thoroughbred horses identified that individuals with OCD lesions had higher blood glucose and insulin concentrations after being fed a grain ration compared to age-matched controls.[145,146] Robles et al[143] evaluated the impact of the maternal environment on foals born to mares that were obese (body condition score ≥ 4.25/5) at the time of their pregnancy and throughout gestation. In this study, obese and nonobese broodmares were maintained on the same management and nutritional regimen and there was no difference in insulin parameters between groups, except at 300 days of gestation when obese broodmares were more insulin resistant with a higher glucose effectiveness. Foals born to obese mares had a higher incidence of insulin resistance at 6 and 18 months of age and OCD at 12 months of age. Notably, there was not a statistically significant difference among foals with OCD lesions at 18 months of age, although approximately 30% of the foals born to obese mares had lesions compared to 10% of the foals born to nonobese mares.

In humans, there is some indication that an active lifestyle and diet modification have beneficial effects on prevention of MetS.[147,148] This is true in horses as well, and some dietary and exercise benefits have been described above. More up-and-coming research in this area, including novel promising therapeutics, can be found in the companion Currents in One Health by Manfredi et al, *AJVR*, February 2023.

Summary

Endocrine disorders represent a one-health issue in which research on treatments and prevention in humans or horses can help inform approaches in the other species, thus improving the health of both. It is critical that veterinarians and doctors of human medicine share information to accomplish this goal. Endocrine disorders are performance-limiting in humans and horses and, in the latter, are likely to contribute to laminitis, back pain, suspensory ligament desmitis, osteoarthritis, and OCD. Symptomatically treating musculoskeletal pain without diagnosing and addressing underlying endocrine disorders can result in more days of performance lost either due to unsuccessful attempts to return to work or later recurrences of the issue in both humans and horses. Clinicians should consider testing for equine endocrine disorders if the horse's age, breed, or performance suggests it could be of concern and develop preventative and/or therapeutic management plans accordingly.

Further studies are needed to determine the increased risk for various musculoskeletal conditions based on endocrine health and the impact on prognosis that concurrent endocrine disorders afford. The interaction between endocrine disorders and equine performance should be investigated in various disciplines and breeds, including establishing whether a metabolic osteoarthritis subtype exists as it does in humans. Assessment of return to work success in horses with concurrent endocrine and musculoskeletal disease in light of treatment plans that address both aspects should be performed.

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