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Review Article

Focus on the epidemiology, pathophysiology, diagnosis, and management of insulin dysregulation in horses

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Abstract:

Because there are various inter-related disorders of insulin metabolism that all may contribute to the final result of hyperinsulinaemia, the phrase "insulin dysregulation" has become the most acceptable term to use when describing equine metabolic syndrome (EMS). Insulin dysregulation is widespread in horses, and it appears to be more prevalent in physically sedentary horses. Laminitis and hyperinsulinaemia have been linked, as have other components of insulin dysregulation. Diagnosis of insulin dysregulation should be done in stages, beginning with basal testing, which includes baseline values of insulin and glucose, and concluding with dynamic tests, which detect tissue insulin resistance and hyperinsulinaemia. Dietary adjustments are the key to weight loss in the majority of EMS horses. To encourage weight loss, the horse should be given around 1.25% of its body weight every day. Exercise not only aids equid weight loss but also improves insulin sensitivity. The exercise should be tailored to the specific horse, taking into account its breed, fitness level, and owner's resources. When an obese horse is unable to exercise owing to laminitis or when obesity persists after extensive exercise and dietary management, levothyroxine sodium and metformin hydrochloride can be given to help accelerate weight loss and increase insulin sensitivity. Insulin dysregulation is a defining feature of equine metabolic syndrome and has garnered attention due to its direct link to laminitis. There is need for an in-depth understanding of ID in order to prevent the development of clinical laminitis. The current study discusses the epidemiology, pathophysiology, diagnosis, and management of insulin dysregulation in horses.

Key words: insulin dysregulation; equine metabolic syndrome, hyperinsulinaemia; insulin resistance; laminitis

Introduction

Insulin in the body maintains homeostasis by regulating glucose metabolism. The diagnosis of equine metabolic syndrome (EMS) is based on establishing the presence of insulin dysregulation (ID). Ever since it has been established that hyperinsulinaemia causes laminitis in horses (Asplin et al., 2007; de laat et al., 2010), researchers have started paying attention to the factors involved in the promotion of a high concentration of inzulin in horses.

The insulin response to oral glucose or sugar may be one of the most important predictors of laminitis risk (Meier et al., 2018), and insulin resistance (IR) is only one driver of hyperinsulinaemia after consuming feed high in non-structural carbohydrates.

The term "insulin dysregulation" captures the spectrum of abnormal insulin metabolism in equine species, including any combination of fasting hyperinsulinaemia, postprandial hyperinsulinaemia (response to consumed feeds, oral sugar test, or oral glucose test), or tissue insulin resistance (Frank and Tadros, 2014). While peripheral insulin resistance is a major contributor to hyperinsulinemia, insulin dysregulation refers to a variety of other conditions that can cause hyperinsulinemia. It's crucial to understand that insulin resistance and hyperinsulinemia are not the same thing. The accepted explanation for hyperinsulinemia is that insulin secretion rises as a result of diminished tissue insulin sensitivity, a condition known as compensated insulin resistance (Treiber et al., 2005). Insulin resistance occurs when insulin-sensitive tissues such as the skeletal muscle, liver, and adipose tissue fail to respond to insulin (Frank and Tadros, 2014).

Laminitis has been a major burden on the equine industry. When horses develop clinical laminitis and become crippled, their dependence on a functional limb becomes more prominent. This is because it takes just one compromised leg for the horse to be rendered unfit for use (Mitchell et al., 2014). Therefore, prevention of clinical laminitis is critical when managing horses with insulin dysregulation. In-depth understanding, early and proper diagnosis, and effective management of ID is required in order to prevent the development of clinical laminitis. The present paper reviews the epidemiology, pathophysiology, diagnosis, and management of ID in horses.

Epidemiology of Insulin Dysregulation

The prevalence of ID (IR and hyperinsulinaemia) has been reported by several investigators. A study carried out in Australia reported 27% of ponies being hyperinsulinemic (Morgan et al., 2014), 22% in the US (Muno, 2009), and in 18% of mature light breed horses also in the US (Pleasant et al., 2013). Carslake et al. (2020), Tavanaeimanesh et al. (2022), and Akinniyi et al. (2023a) reported a prevalence of 23.3% in the US, 2.5% in Iran, and 43.10% in Nigeria, respectively. Insulin sensitivity can also vary by breed, as evidenced by the fact that Andalusian horses and ponies have lower insulin sensitivity than Standardbred horses (Bamford et al., 2014).

Insulin dysregulation appears to be more common among physically inactive horses, which is likely due to exercise's favourable influence on insulin sensitivity as well as weight loss via higher energy expenditure (Liburt et al., 2011). Insulin levels in elderly horses and ponies are said to be much higher than in younger horses and ponies (Morgan et al., 2014; Rapson et al., 2018). However, sex does not seem to influence most markers of ID in normal or laminitic horses and ponies (Cartmill et al., 2006).

Pathophysiology of Insulin Dysregulation

Excessive non-structural carbohydrate consumption causes a prolonged glucose influx into the bloodstream. This puts constant pressure on the insulin-sensitive glucose transporters (GLUT4), which are in charge of the uptake of glucose in peripheral tissues (Joost and Thorens, 2001). The glucose transporters become exhausted and resistant to insulin activation over time, requiring higher insulin concentrations to drive them thereby maintaining a normal concentration of glucose in the blood (Bloomgarden, 1998). As a result of the increased need for insulin, laminitis develops when the insulin concentration in the blood reaches toxic levels. In ponies, oral glucose administration stimulates more insulin production than IV glucose administration (de laat et al., 2016), showing that the gastrointestinal tract produces substances that enhance glucose-induced pancreatic insulin secretion.

In the horse, at least 3 hormonal factors, also known as incretins, exist: glucagon-like peptides 1 (GLP-1), glucagon-like peptides 2 (GLP-2), and gastric inhibitory polypeptide (GIP) (Durham et al., 2019). The relative contribution of these incretins to insulin production varies greatly between species, with GIP, GLP-1, and glucose having a 2%, 23%, and 76% influence on insulin response to oral glucose delivery in horses, respectively (de laat et al., 2016). In horses, active GLP-1 promotes insulin secretion (de laat et al., 2016), even though its involvement in ID is unknown (Frank and Walsh, 2017). Glucagon-Like Peptide 2 is another incretin that does not affect insulin secretion directly, although it does improve glucose absorption through gastrointestinal effects. Its function in EMS is similarly unknown (de laat et al., 2018). When compared to forage or fat-rich diets, chronic feeding of a diet high in non-structural carbohydrates (NSCs) has been reported to impair insulin sensitivity and adiponectin concentrations (Hoffman et al., 2003; Treiber et al., 2005; Bamford et al., 2016). However, the link between dietary NSC intake and IR is not clear. New research suggests that switching to a high-NSC diet can increase glucose tolerance and tissue insulin sensitivity while causing an exaggerated postprandial insulinemic response (Bamford et al., 2016).

Diagnosis of Insulin Dysregulation

Insulin dysregulation can be diagnosed by demonstrating tissue insulin resistance or hyperinsulinaemia (pre-prandial or postprandial). Some horses develop IR without hyperinsulinaemia, others develop hyperinsulinaemia without IR, while yet others have both IR and hyperinsulinaemia. As a result, it may be recommended that the diagnosis of insulin dysregulation be done in stages, beginning with basal tests, which include baseline values of insulin and glucose, and finally with dynamic tests, which diagnose tissue insulin resistance and hyperinsulinaemia.

1) Basal Testing

A) Insulin

Basal insulin concentration is a convenient screening test for hyperinsulinaemia. An indication of insulin dysregulation can be established after establishing resting or basal hyperinsulinaemia. However, a negative result does not rule out the presence of insulin dysregulation (Frank et al., 2010). It is, however, no longer recommended to fast horses before measuring basal insulin concentration because it further decreases the sensitivity of the test. Due to the lack of standardisation of responses, measuring serum insulin within 4-5 hours of giving grain to horses is also not recommended (Durham et al., 2019). Serum insulin concentrations assessed in ponies 1-3 hours after coming off pasture could be used to distinguish horses prone to laminitis using a 20 μIU/mL cut-off for insulin (Carter et al., 2009). Resting insulin levels can also be assessed in forage-fed animals, though the effects of different forages and intake rates will influence the results.

Haylage feeding was linked to higher peak insulin levels (up to 66.0 μIU/mL) in these healthy ponies (Carslake et al., 2018). When feeding forage of unknown quality, small elevations in resting insulin concentrations (20–50 μIU/mL) should be suspected of ID, and dynamic testing with an oral sugar test (OST) or oral glucose test (OGT) is advised (Durham et al., 2019). The range of laboratory assays now utilised to assess equine insulin concentration adds to the issues associated with basal serum insulin concentration (banse and Mcfarlane, 2014).

B) Glucose

Horses with EMS rarely have hyperglycaemia. This is because the pancreas hardly gets exhausted in the release of insulin into the blood (Durham et al., 2009). Nevertheless, blood glucose concentrations are mostly within the normal range, though at the higher end of the range, indicating partial loss of glycaemic control. If detection of hyperglycaemia becomes persistent, diabetes mellitus should be suspected (Frank et al., 2010). In horses, type 2 diabetes mellitus is not known to be common (Durham et al., 2009). Hyperglycaemia may be considered in the diagnosis of insulin dysregulation when it cannot be attributed to other possible causes like recent feeding, stress, inflammatory processes, and administration of a-2 agonist drugs (e.g., xylazine, clonidine, romifidine, detomidine, medetomidine, and dexmedetomidine).

2) Dynamic Testing

A) Oral Sugar Test (OST)

The oral sugar test (OST) examines the glucose-induced insulin response to non-structural carbohydrates administered orally (Hoffman et al., 2003). According to Schuver et al. (2014), a diagnosis of hyperinsulinemia with the OST is based on serum insulin > 60 μIU/mL 60 or 90 minutes after oral administration of 0.15 mL/kg corn syrup to already fasted horses (between 3 and 12 hours) (Knowles et al., 2017) using radioimmunoassay (RIA). Fasting of horses is frequently achieved by leaving one flake/slice of hay with the horse before midnight, followed by the test the next morning (Durham et al., 2019). In another trial, using the same assay, a lower cut-off of > 45 µIU/mL was recently recommended (EEG, 2022). This test accounts for the enteroinsular axis and measures the insulin response to an oral carbohydrate dosage (DE LAAT et al., 2016). With a cut-off of > 30 µIU/mL between 60 and 90 minutes using Coat-A-Count RIA, a larger dosage of 0.25 mL/kg BM corn syrup was proposed to improve diagnostic value (Manfredi, 2016). With a value of > 110 µIU/mL determined by RIA at 60 minutes and an even larger dosage of 0.45 mL/kg BW corn syrup, it was found to provide increased sensitivity for ID and successfully distinguish 3 ponies with no history of laminitis from 5 previously laminitic ponies (Jocelyn et al., 2018). However, the findings of this trial may be difficult to interpret because it has been observed in a few other studies to have poor repeatability, with a coefficient of variance as high as 40% (Smith et al., 2016).

B) Oral Glucose Test (OGT)

An oral glucose test (OGT) has been created for places in the world where corn syrup is not frequently available (Jose-Cunilleras et al., 2002). Fasting overnight before the test is recommended, both to promote compliance with taking the test dose and to facilitate glucose transit through the stomach (Durham et al., 2019). The method of glucose administration varies. In some studies, powdered dextrose is mixed with chaff and/or bran and eaten by the horse spontaneously (in-feed oral glucose test), whereas, in others, glucose is delivered as a solution through a nasogastric tube (Pratt-Phillips et al., 2015).

In the in-feed oral glucose test, 0.5 or 1.0 g/kg body mass (BM) glucose powder is mixed into small, low-glycaemic meals (Jeffcott et al., 1986; Meier et al., 2018). Peak plasma glucose levels occur 60 to 120 minutes after a meal (Smith et al., 2016). The protocol's main drawback is that the high glucose dose can be unpleasant to swallow; test findings might be influenced by ingestion duration, stomach emptying, and intestinal absorption (de laat and Sillence, 2017). On the other hand, a recently published dosage of 0.75 g/kg BM, on the other hand, produced satisfactory results and boosted ponies' acceptability (de laat and Sillence, 2017). Insulin values considered diagnostic of ID are >68 µIU/mL for 0.5 g/kg BM glucose and >80-90 µIU/mL for 1.0 g/kg BM glucose when analysed with the Immulite 1000 chemiluminescent assay at 120 minutes post-feeding (Bertin and de laat, 2017; Knowles et al., 2017). If sedation or physical restraint are not required, the OGT can be conducted using 1.0 g/kg BM glucose dissolved in 2L of water and delivered by nasogastric tube (Warnken et al., 2018). Using the equine optimised insulin enzyme-linked immunosorbent assay (ELISA), the indicated cut-off value for this test protocol is 110 µIU/mL insulin at 120 minutes (Warnken et al., 2018).

Regardless of the administration method, the OGT has higher repeatability than the OST, with a coefficient of variability of about 20%, and the two tests agree on dichotomous results in 85% of cases (Smith et al., 2016). The convenience of this test and the capacity to precisely define the dose of glucose administered (corn syrup glucose content is proprietary information) may have a beneficial impact on its repeatability. Furthermore, it has been suggested that the glucose may be replaced with sweet feed or grain, thereby increasing the test's popularity and adoption (de laat and Sillence, 2017). However, further investigation is needed in this area.

C) Insulin Response Test (IRT)

An insulin response test (IRT), also known as an insulin tolerance test (ITT), has two versions, namely a complete test and a short test (Caltabilota et al., 2010; Bertin and SOJKA-Kritchevsky, 2013). The complete test (complete insulin-response test) is a method that involves injecting soluble insulin as a bolus into the bloodstream in doses ranging from 0.02 to 0.125 IU/kg BW, followed by serial blood collection over 3 hours to determine tissue insulin sensitivity (Caltabilota et al., 2010). The area under the glucose curve is determined, or the insulin dose required to achieve a 50% drop in glucose concentration is recorded.

The short test (2-step insulin-response test) involves measuring blood glucose concentration before and 30 minutes after administering a 0.1 IU/kg BW soluble insulin IV injection. Within 30 minutes, insulin-resistant horses fail to achieve a 50% drop in blood glucose concentration.

With a coefficient of variation of 9%, the complete IRT is as good as or better than most commonly employed methods of measuring tissue insulin resistance in horses (Caltabilota et al., 2010). Furthermore, excellent agreement has been demonstrated between the complete and short versions of the tests, implying that the short version of the insulin response test might be employed in the field (Bertin and Sojka-Kritchevsky, 2013). The IRT has the advantage of not requiring pre-test fasting, and blood glucose concentrations can be monitored with a glucometer, allowing for preliminary results to be obtained on the farm.

The cost of insulin and the risk of developing clinical hypoglycaemia are both disadvantages (even though this is unlikely to happen in horses chosen for testing on suspicion of ID). To further reduce the risk of hypoglycaemia, a moderate amount of grain or dextrose can be given to the horse immediately after the 30-minute sample is taken (Bertin and Sojka-Kritchevsky, 2013).

D) Combined Glucose-Insulin Test (CGIT)

The combined glucose-insulin test (CGIT) consists of an IV administration of 150 mg/kg BM glucose followed by an IV injection of 0.1 IU/kg BM neutral (regular) insulin (Eiler et al., 2005). Both glucose and insulin are measured in the basal sample and after 45 and 75 minutes in a shortened protocol (Morgan et al., 2016). A biphasic blood glucose curve is seen in healthy horses, with hyperglycaemia followed by a negative phase in which glucose declines below the initial baseline concentration. In most cases, glucose concentrations should return to baseline within 45 minutes. When using the Coat-A-Count radioimmunoassay (RIA), the insulin concentration should be < 20 µIU/mL both at baseline and at 75 minutes, and < 100 µIU/mL at 45 minutes (Eiler et al., 2005). Insulin dysregulation is characterised by hyperinsulinemia and a prolonged recovery time to baseline glucose concentration. Although the CGIT is normally well tolerated, hypoglycaemia can develop, and horses that have been tested should be continuously watched with additional glucose injections or a small feed readily available.

Management of Insulin Dysregulation

1) Dietary Management

In most horses with EMS, dietary changes are the key to weight loss. It's crucial to get a complete history from the owner about the horse's current feeding regimen and management, including grazing, exercise, and confinement choices. Adjusting the diet to the horse's specific demands improves owner compliance and results in a greater response to treatment (Morgan et al., 2016).

The very first step is the removal of concentrate feed, as well as any high-sugar treats like apples, from the diet. The diet should be based on forage, with low-to medium- non-structural carbohydrates (NSC) forage having an NSC level of less than 10% (Frank et al., 2010). Simple sugars and starches are examples of non-structural carbohydrates (NSC), which are commonly found in plant seeds and leaves. When given ad lib access to feed, horses eat approximately 2 to 2.5% (NRC, 2007) and ponies close to 5% (Argo et al., 2012) of their body weight in dry matter (DM) per day. The horse should be fed approximately 1.25% of their body weight in DM (approximately 1.5% in fresh weight for hay with 80 to 85% DM) per day to induce weight loss. Because of potential issues with hindgut function, protein restriction, stereotypies, and hyperlipaemia, diets containing less than 1% of bodyweight DM are not recommended (Mcgregor-Argo, 2009). For proper recommendations, the NSC content of available forage should ideally be determined, and several feed companies provide this service commercially.

In the absence of this knowledge, soaking the hay is a simple and widely suggested means of lowering the NSC content. Watts and Chatterton (2004) found that soaking hay in cold water for about 60 minutes reduces the water-soluble sugar content by about 30%, whereas soaking for 8 to 16 hours reduces the water-soluble sugar content by up to 50% (Longland et al., 2011; Mack et al., 2014). Soaking also depletes water-soluble microminerals, which must be replaced (Mack et al., 2014). Hay soaking can result in DM losses of up to 25% (Argo et al., 2015); hence, it should only be done with large amounts of feed or under strict veterinary supervision. Soaking haylage is not recommended due to the possibility of increased bacterial fermentation.

To provide the overall daily requirements of vitamins and minerals, a commercial, high-quality balancer should be supplied. Low-calorie balancers are not suggested because they generally have a greater protein restriction than a calorie restriction. A low-NSC diet (chaff-based) combined with a complete balancer is given to horses that do not enjoy eating hay that has been soaked in water or given due to the convenience of the owner (Dugdale et al., 2011).

Weight loss in pastured ponies and horses can be very hard and unproductive since caloric intake is tough to quantify. To promote initial weight loss, it is often advisable to put the animal in a stable. Following improvement or normalisation of their CGIT findings, many horses and ponies can be returned to controlled grazing, utilising sand maneges, bare fields, or a grazing muzzle (Morgan et al., 2016). However, owners should be advised on how to properly fit and handle a grazing muzzle. Strip grazing or short intervals of grass availability can be counterproductive since ponies with limited grazing have been found to rapidly compensate by ingesting nearly half of their daily DM intake within 3 hours of grazing (Ince et al., 2011).

2) Physical Exercise

Exercise not only helps horses lose weight but also increases insulin sensitivity (Akinniyi et al., 2023b). Insulin sensitivity improved in ponies who exercised on a treadmill for 6 weeks, and this improvement was sustained even after 6 weeks of deconditioning (Freestone et al., 1992). Ungru et al. (2013) found that dietary restriction coupled with exercise improved insulin sensitivity in obese insulin-resistant ponies, while mild exercise alone may not be enough (Carter et al., 2010). In horses with EMS, exercise must be limited if they have acute or chronic active laminitis, and it can be quite dangerous in an unstable situation. However, activity should commence as soon as the horse is free of all anti-inflammatory and analgesic medications.

The exercise should be adapted to the particular horse, taking into account its breed, fitness level, and the owner's facilities. Short periods of exercise on a soft surface, such as a manege, may be useful to begin with. There is little evidence on the ideal strategy, but to maximise glycogen utilization, exercise should continue up to 15 minutes of trotting per day (Hodgson et al., 1985). A flare-up of laminitis or increasing pain should be continuously monitored. Even though pasture turnout may not be enough to increase insulin sensitivity (Turner et al., 2011), confinement can be a trigger factor for laminitis in horses with EMS (Wylie et al., 2013). As a result, any reduction in exercise in EMS horses should be carefully monitored for concomitant caloric restriction.

3) Pharmacological Intervention

Horses with EMS are also managed with two medical therapies, both of which have special purposes.

A) Levothyroxine Sodium

When significant insulin dysregulation (ID) is present in an obese horse who is unable to exercise due to laminitis or when obesity continues despite intensive exercise and diet management, this medication can be used to help speed up weight loss. In addition, levothyroxine sodium, administered in feed or by mouth, at a dosage of 0.1 mg/kg BW once a day, reduces body weight and increases insulin sensitivity in horses (Frank et al., 2008). If obesity persists after 3 months of treatment, a higher dosage of 0.15 mg/kg BW can be chosen. Levothyroxine is given until the horse's body condition score reaches an ideal level, or until the conclusion of six months. When treatment is stopped, the dose is reduced to 0.05 mg/kg BW/day for 2 weeks, then to 0.025 mg/kg BW/day for another 2 weeks. Although some horses display mild hyperexcitability and increased activity, no complications have been reported when given levothyroxine for a year (Frank et al., 2008). When horses are given levothyroxine, pasture access must be limited to prevent the horse from overfeeding itself.

B) Metformin Hydrochloride

This is often used to treat diabetes mellitus in humans, but it's also been shown to treat ponies and horses with resting insulin levels and proxy measures of insulin sensitivity (Durham et al., 2009). Insulin sensitivity was found not to improve when IV glucose tolerance tests were done to measure insulin and glucose dynamics in equine species (Tinworth et al., 2012). The low oral bioavailability of metformin in equids (Hustace et al., 2009), and recent findings demonstrating that metformin operates at the gut level to blunt blood glucose and insulin concentrations after feeding, may explain this discrepancy (Rendle et al., 2013). Metformin appears to be better suited to regulating postprandial hyperinsulinaemia in horses than it is to treating IR. Metformin is currently recommended at 30 mg/kg BW PO every 8–12 hours, one hour before feeding or turning out (Frank and Tadros, 2014).

Conclusion

Insulin dysregulation is a defining feature of EMS. Insulin dysregulation (ID), insulin resistance (IR), and hyperinsulinaemia are not interchangeable terms. Hyperinsulinaemia and laminitis have been linked. Laminitis is a common condition that causes horses to be lame. The tests used to diagnose ID are classified as basal testing and dynamic testing. Exercise not only aids equid weight loss but also improves insulin sensitivity. The reduction of concentrate feed is the initial step in the dietary management of ID. When a horse with severe ID is unable to exercise owing to laminitis or when obesity persists after extensive exercise and diet management, levothyroxine sodium and metformin hydrochloride are remedies to help accelerate weight loss and enhance insulin sensitivity.

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