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Nutritional considerations for the management of equine pituitary *pars intermedia* dysfunction

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Abbreviations: ACTH = adrenocorticotropic hormone; BCS = body condition score; BW = bodyweight; EMS = equine metabolic syndrome; ID = insulin dysregulation; NSC = non-structural carbohydrates; PPID = pituitary *pars intermedia* dysfunction.

Summary

Pituitary *pars intermedia* dysfunction (PPID) is a common endocrine disorder affecting equids. To help achieve and maintain healthy body condition, whilst reducing the risk of dietary associated laminitis, appropriate nutritional management is key. This review proposes a stepwise approach to building an individual nutritional plan for equines with PPID. Starting with considerations relating to current and desired body condition and muscle mass, it highlights the importance of providing appropriate amounts and forms of energy, carbohydrate and protein; with further practical considerations regarding the feeding of animals that are often aged and may have particular clinical sequelae to PPID. The next important step is to determine the degree of insulin dysregulation (ID), as this is a major factor associated with an increased risk of laminitis. Animals with ID should be fed low Non-Structural Carbohydrate (NSC) providing feeds/feedstuffs as well as grass and forage with NSC content <10-12% on a DM basis. Finally, adjustments need to be made according to life stage and activity level.

1. Introduction

Pituitary *pars intermedia* dysfunction (PPID) is a common endocrine disorder affecting various equid species including domestic horses, donkeys, Prezwalski's horses and zebras (Secombe et al., 2018; Shotton et al., 2018; Mejia-Pereira et al., 2019). The shift away from domestic horses having an essential working role, in combination with improved husbandry, nutrition and veterinary care, has seen an increasing number of long-lived horses worldwide (Ralston and Harris, 2013). The chronic, progressive nature of PPID means that increasing age is a risk factor for its development, with a reported prevalence of over 20% in horses older than 15 years (Ireland and McGowan, 2018) and over 25% in horses older than 20 years old (Ballou et al., 2020).

The pathophysiology of PPID is related to progressive degeneration of dopaminergic neurons from the hypothalamus, resulting in a loss of tonic inhibitory control over melanotrope cells of the pituitary *pars intermedia* (van der Kolk et al., 2004; McFarlane, 2011). Melanotrope hyperplasia and eventual adenoma formation within the *pars intermedia* is in turn associated with increased production of pro-opiomelanocortin derived peptides, including adrenocorticotropic hormone (ACTH). Measurement of immunoreactive ACTH is widely used as the primary laboratory diagnostic marker of PPID (Orth and Nicholson, 1982; Dybdal et al., 1994; Couëtil et al., 1996; McGowan et al., 2013a).

Reported clinical signs of PPID are varied and include hypertrichosis/hirsutism, weight loss, abnormal fat redistribution, muscle wastage/atrophy, lethargy and depression, polyuria/polydipsia, and concurrent infectious diseases (McGowan et al., 2013b; McFarlane, 2014; Ireland and McGowan, 2018; Horn et al., 2019). Laminitis is commonly reported in PPID cases (Ireland and McGowan, 2018). This potentially devastating condition is thought to occur predominantly in PPID cases with insulin dysregulation (ID), although the specific link between PPID and ID has not been fully elucidated (McGowan et al., 2004; Tadros et al., 2019). Studies have shown that PPID is not always associated with ID and that impaired insulin sensitivity may reflect the older age of most PPID animals rather than being linked to PPID per se (Jacob et al., 2018a; Mastro et al., 2015; Rapson et al., 2018). Tadros et al. (2019) suggested that there are three possible explanations for the relationships between PPID and ID: (1) ID is a marker of PPID chronicity, (2) ID and PPID are independent disorders, or (3) that pituitary dysfunction exacerbates or induces the development of ID. In the latter, the authors refer particularly to animals with a genetic predisposition or environmental risk factors for ID, plus the influence of high concentrations of pituitary hormones on the pancreatic β-cell response (Beloff-Chain et al., 1983), as well as a reduction in hepatic clearance of insulin that is associated with PPID and/or ageing (Toth et al., 2010). Further work is required to investigate these relationships.

The mainstay of pharmacologic treatment for PPID is the administration of pergolide mesylate, a dopamine receptor agonist that has been shown to result in clinical improvement (Pongratz et al., 2010; Rohrbach et al., 2012; Schott et al., 2019; Tatum et al., 2020), although there is not yet enough evidence to show that treatment specifically reduces the risk of laminitis (Knowles, 2019). Nutrition is also key, and an appropriate dietary plan should be incorporated into the long-term management of PPID cases. It is important to note that diet, especially starch-rich rations, can influence ACTH results (Jacob et al., 2018b).

Current recommendations mostly relate to the general guidelines for aged or geriatric animals (Ralston and Harris, 2013; Jarvis et al., 2019), rather than specific advice for those with PPID. The purpose of this review was to provide recommendations for the nutritional management of horses and ponies with PPID. We focused on key aspects such as body condition and insulin responsiveness; although it is appreciated that in individual cases other details such as hoof care and specific co-morbidities (e.g. respiratory tract conditions, gastrointestinal conditions or hepatic dysfunction) need to be considered when developing the final dietary plan (Geor et al., 2013; Harris and Shepherd, 2021).

2. Nutritional Considerations for the Management of PPID

Before developing a nutritional plan, a number of factors need to be considered, such as the current feeding regimen, resources and facilities available, clinical history and presence of any co-morbidities, as well as owner expectations (Hesta and Shepherd, 2021). In PPID cases in particular, key points to consider include: body condition, the presence or absence of ID (and potentially the severity of ID), age and activity level (Figure 1). Whilst the management of these factors may interlink, it can be helpful to consider these in a systematic way when developing dietary recommendations. Continual monitoring and adjustments will be required, especially as PPID-affected animals age.

2.1 Body Condition

Body condition scoring (BCS) evaluates fat deposition at specific anatomical sites. There are several BCS systems used globally, typically a 0-5 (Carroll and Huntington, 1988) or 1-9 scale (Henneke et al., 1983). These systems do not specifically evaluate muscle mass, although in practical terms, animals with low body condition often have some degree of muscle loss. Familiarity with whichever system is being used is important, as well as applying it in a consistent manner (Dugdale et al., 2012). The authors recommend use of the 1-9 scale originally developed by Henneke and modified by Kohnke (1992), which offers descriptors for six key body areas independently scored through palpation. Regardless of the system used, it is important that animals with PPID are monitored regularly through palpation, especially as body condition is more difficult to assess in equids with long hair coats. Body mass index determinations, which are popular in human medicine, do not appear to be very accurate in the horse (Carter et al., 2009), but alternative systems which rely on more objective morphometric measurements are being developed, such as a body condition index (Potter et al., 2015).

Overweight/obese animals

Individuals with a BCS of 6-7/9 can be considered 'overweight' and those with a BCS of ≥7/9 can be classified as 'obese' (Dugdale et al., 2012). In essence, the key principles of nutritional management of an obese PPID case remain the same as for all obese animals (Geor and Harris, 2013). For an overweight individual with PPID, additional factors may need to be taken into consideration such as the time of year and their propensity to lose or gain weight. Allowing elderly animals with PPID that typically lose weight over the winter, to enter winter with a BCS of 6/9 may be beneficial. However, if the animal has a tendency to gain weight in warmer months, it may not be ideal to reach the end of winter with a BCS of 6/9.

General considerations for weight management are discussed in more detail elsewhere (Argo et al., 2012; Geor and Harris, 2013; Argo et al., 2015; Rendle et al., 2018; Shepherd et al., 2021). The key practical management strategies for obesity include: (1) promotion of weight loss and improved insulin sensitivity via dietary restriction and, where possible, an increase in physical activity; and (2) avoidance of feeds that may exacerbate insulin dysregulation (feeds rich in non-structural carbohydrates [NSC; starch, sugars, fructans] such as grains, high starch containing feeds and 'lush' or stressed pasture forages). Adjunct pharmacological treatment with levothyroxine sodium could be useful in the management of cases with weight loss resistance, although its use should be carefully considered in horses with PPID due to potential catabolic effects. The nature of any weight loss programme will need to be targeted to the individual animal and the resources of the owner/carer.

There are a number of factors to consider when developing a weight management plan including:

- **Acceptance:** Owners/carers first need to recognise that their horse is overweight/obese and that a weight loss programme is necessary.
- **Commitment:** Owners/carers must appreciate that a weight loss programme requires time and commitment, requiring ongoing support from their veterinary team, including regular adjustments based on re-evaluation of body condition (Morgan et al., 2016).
- **Resources:** To successfully implement any weight loss programme, any real or perceived barriers to implementation need to be considered. These barriers could include owner concerns over the use of grazing muzzles, balancing the risks

associated with obesity vs. dietary restriction, ground suitability for track systems, the practicalities of strip grazing and the provision of environmental enrichment. Management plans should be developed on a case-by-case basis, considering the welfare, health and behaviour of the animal, as well as their suitability for a particular client to implement (Furtado et al., 2021).

- **Changes:** The weight loss program will need to consider the current feeding and management regimen. For some horses, replacing an inappropriate (e.g. high energy containing) complementary feed with a forage balancer may be all that is required, whereas other horses may require more drastic changes from the start, especially if they have suffered from laminitis.
- **Expectations:** The aim of any weight loss plan should be to achieve a <u>maximum</u> amount of 1% bodyweight loss per week after the first week (as during the first week any weight loss may be due to reduced gut fill). A more realistic target (which can still be difficult to achieve in weight loss resistant cases) is a weekly weight loss of 0.5% (after the first week).
- **Monitoring:** In very obese animals, BCS may not change in the initial phases of the weight loss programme (Dugdale et al., 2010). This may not only be very demoralising for the owner/carer but may also promote more strict energy restrictions than may be necessary. The inclusion of additional monitoring modalities, such as measurement of belly girth or rump width into the plan may be beneficial to gauge progress.
- **Foraging:** The extension of foraging time is an important behavioural consideration in horses that are provided with restricted amounts of forage. So whilst small mesh single/doubled haylage nets and/or splitting hay into multiple small nets (placed around the stable area) can be advantageous, tripled nets may promote frustration and increase pressure on the neck (Ellis et al., 2015), which may be contraindicated in older animals with cervical arthritis. Ground based 'slow-feeders' may provide practical alternatives to extend intake time and reduce frustration (Rochais et al., 2018).
- **Supplementation:** A broad-spectrum vitamin, amino acid and mineral supplement will be needed if reduced levels of complementary feed are given (or if forage is the main component of the diet) and especially when feeding soaked forage.

In addition, there are perhaps extra considerations when managing an obese animal with PPID:

- Muscle is typically lost during weight management programmes and this may be even more relevant to horses with PPID, especially if they are older. Therefore:
    a. it is essential to discuss and agree on any increase in structured exercise, including a plan designed to help muscle development.
    b. it is necessary to evaluate the quality and quantity of protein intake (see section 3.1).
- Typically, to reduce calorie intake, recommendations are made to change to a more mature forage and/or replace some of the forage with good hygienic quality straw (Harris et al., 2017). This needs to be adjusted for the individual, considering any dental issues either currently present or likely to develop given the age of many animals with PPID. Any such forages may need to be introduced slowly and animals monitored carefully with respect to the development of problems such as impaction colic or choke. Alternative forages that are low in starch and sugar may need to be contemplated.
- Practically, it may be prudent to assume that obese animals with PPID have, or are at risk of developing, ID and their nutrition should be managed appropriately (see section 2.3).

Underweight animals

While obesity tends to develop in animals, due to the simple fact of higher energy intake compared with expenditure, the reasons for loss of condition in underweight animals are often multifactorial, especially in older animals with PPID. The co-morbidities of underweight animals are outside the scope of this review, and readers are referred to the work of Tamzali (2006) or Jarvis & McKenzie (2021). A full and detailed history plus clinical evaluation is required, as well as a detailed inspection of the feeding and management regimen, and an assessment of suitability for that individual. The appraisal of BCS is a key part of the clinical evaluation, especially because owners may not recognise the underweight status of horses with PPID (Kienzle and Bockhorni, 2018). The dietary and management plan then needs to be tailored to any specific underlying cause(s) of weight loss (Jarvis and McKenzie, 2021).

Specific aspects to consider when managing underweight animals with PPID include:

- Loss of weight/condition may be slow and gradual, and potentially accepted as normal in older animals, and not recognised until relatively severe. Animals that have previously been good doers may no longer thrive on a restricted ration as they age and/or develop PPID. Simple changes in the diet formulation, energy content and frequency of meals may address some of these issues.
- Lean animals may still develop ID and this, coupled with the increasing likelihood of insulin resistance in older animals, means that assessing and monitoring for ID becomes even more relevant.
- Because many animals with PPID are older, there should be an emphasis on conditions that tend to become more prevalent with age, such as osteoarthritis (not just in limbs but also in the neck and jaw) and dental conditions. It is important to observe the individual whilst it eats, not only complementary feed, but also any long stem forage (including grass where quidding may be missed if co-grazers have learnt to eat the quids). Appropriate dental correction, if possible, and/or changes to formulation of the feed can then be made as required.
- Horses with PPID may be more susceptible to endoparasite infestations, and monitoring of faecal egg counts, and strategic deworming should be incorporated into any management protocols (McFarlane et al., 2010; El-Hage et al., 2019).
- Aged animals *per se* may have thermoregulatory issues which may promote either increased energy expenditure/requirements (to maintain body temperature) (Cymbaluk and Christison, 1990); or decreased food intake (due to overheating exacerbated potentially by hypertrichosis) (Morgan, 1997). Colder temperatures may also exacerbate osteoarthritis, restricting the ability of horses to move and forage. Frozen water may also contribute to inappetence if soaked feeds become too cold, or palatability may be reduced if feeds have been left too long in hot weather.
- Low body condition may be associated with more vigilant animals or those whose foraging is frequently interrupted (due to herd dynamics) (Giles et al., 2020). This may be practically managed by providing extra feed/forage to individuals, including creating simple corals/feeding stations in fields. However, it is important to recognise that some horses may not feed as well on their own or if separated from a ‘bonded’ companion.

Muscle atrophy

Weight loss and reduced muscle mass (atrophy), primarily in the epaxial and gluteal musculature, termed “sarcopenia” when related to ageing (Larsson et al., 2019), is often present in animals with PPID (Thompson, 2009). New muscle atrophy scoring systems specifically focused toward older horses with PPID are currently under development (Alisa Herbst, University of Kentucky, personal communication). Previous studies of muscle atrophy in horses with PPID have revealed atrophy of type 2 fibres and increased proteolysis (Aleman et al., 2006; Aleman and Nieto, 2010), and more recently muscle wastage and protein degradation in horses with PPID have been related to the upregulation of the ubiquitin-proteasome system (Banse et al., 2021). However, PPID does not appear to significantly alter protein metabolism nor the postprandial activation of protein synthesis (Mastro et al., 2014), despite suggestions that ageing may produce an altered response to feeding with respect to amino acids (Mastro et al., 2014). Even though the cause of muscle atrophy in PPID has not yet been elucidated, it is commonly reported and should be a factor to consider when the diet is formulated (see section 3.1).

Monitoring plan

After realistic goals have been set, body condition and weight should be monitored regularly (i.e. every 2 – 4 weeks) under identical conditions. Once the target body condition (ideal BCS 5/9) and weight (Catalano et al., 2016; Catalano et al., 2019; Shepherd et al., 2021) have been achieved, an appropriate weight maintenance programme is recommended to avoid a return to weight gain or loss. This should include monthly assessment of body condition and weight to ensure that not only is the feeding program appropriate to the current level of physical activity and other influences on energy requirements (e.g. ambient conditions such as temperature, wind, rain [Cymbaluk and Christison, 1990]) but also to detect any other issues (e.g. behaviour problems, herd dynamics) that may be developing. A combination of regular BCS assessments by an experienced practitioner and periodic weight measurements using a calibrated weigh bridge can be invaluable. These should be linked with owner/carer weekly determinations of morphometric measurements such as heart girth, belly girth and rump width (Dugdale et al., 2010; Argo et al., 2012).

2.3 Insulin Dysregulation (ID)

Insulin dysregulation is a collective term for tissue insulin resistance, basal and/or postprandial hyperinsulinaemia (Frank and Tadros, 2014), which has been reported to affect approximately one-third of horses with PPID (McGowan et al., 2013b). Various dynamic testing protocols such as the oral sugar test or insulin tolerance test can be used to characterise ID (Bertin and De Laat, 2017; Knowles et al., 2017). Recommendations for the management of animals with ID are aimed at the mitigation of postprandial hyperinsulinaemia, including the restriction of access to grass and forage with NSC contents >10-12% on a DM basis (Geor and Harris, 2013). Recent work has suggested that severely insulin dysregulated animals can have exaggerated insulinaemic responses to even small intakes of complementary feeds, with a threshold of between 0.08-0.15g NSC/kg BW (Macon et al., 2021). Practically, based on this work, severely insulin dysregulated animals should be restricted to 0.1g NSC/kg BW per meal if a very low insulin response is required. In older animals with age-associated increases in insulin responses, based on the work of Jacob et al. (2018), levels could be increased to ~0.5gNSC/kg BW/meal in most individuals. However, because insulin responses are highly variable, and we do not know all of the nutritional triggers for postprandial hyperinsulinaemia, it is advisable to monitor the actual insulin response to the specific meal/forage being fed to a particular individual.

Considerations of note for animals with PPID include:

- Haylage may promote a greater insulin response for a given level of consumed NSC in animals with ID (Carslake et al., 2018), and may negate the potential advantages of increased palatability, improved digestibility and softer structure for horses with poor dentition. Ideally, analysis of forage should be undertaken, and assessment of individual insulin responses to the feeding of haylage (or any other feed) may also be valuable.
- Increased insulin responses after 4 hours of pasture grazing in horses with ID have recently been demonstrated (Fitzgerald et al., 2019); but this needs to be balanced with the potential adverse effects of lack of movement if horses are confined to a stall or small yard. Alternatives such as the use of appropriately fitted grazing muzzles during turnout can be considered.
- As PPID-affected animals age, it is recommended to check for ID regularly (e.g. every 6 months) to detect any changes in glucose and insulin dynamics. This will provide the chance to adapt diet and management practices to reduce the risk of laminitis occurring.

- Regular exercise can improve insulin sensitivity and might help to preserve muscle mass during dietary restriction, even at relatively low intensities (Bamford et al., 2019; Moore et al., 2019). Optimal prescriptive exercise regimens have not been determined, but it is recognised that the more exercise that can be undertaken the better, provided there are no contraindications and that horses are carefully monitored for signs of lameness (Durham et al., 2019).
- Preliminary evidence suggests that essential fatty acid (EPA and DHA) supplementation may improve ID (Hess et al., 2013); however, more work, including in animals with PPID, is required before concrete recommendations can be made.
- The loss of water-soluble carbohydrates (WSC) when soaking forage is variable. Water temperature and duration of soak influences the loss of WSC and other nutrients, as well as the level of microbial contamination (Longland et al., 2014; Moore-Colyer et al., 2014). Advice on soaking forage includes the following:
    - Ideally source low-NSC hay (<12% DM basis), with soaking to be used as an adjunct.
    - Soak for at least 6 hours in cold water (8°C) or 1-3 hours in warmer water (16°C).
    - WSC loss is unpredictably variable and can range from 10% to 40%. Ideally, analysis should be undertaken post-soaking (which may not always be practical).
    - Soaking will cause a loss of DM (practically, allow for 20% loss) plus some soluble protein and a proportion of certain vitamins, minerals, and trace elements. Therefore, a forage balancer should be provided when feeding soaked forage.
- Adjunct pharmacological treatment with metformin, which might reduce postprandial insulin responses (Rendle et al., 2013), can be considered in cases with severe ID in which dietary or management factors cannot be optimised (e.g. cannot avoid pasture turnout; hay cannot be soaked). Further evidence for the efficacy of metformin in horses with ID and/or PPID would be helpful to guide treatment recommendations.

2.3 Laminitis

Endocrinopathic laminitis (associated with ID) was present in 10% of PPID cases evaluated in one study (de Laat et al., 2019), while another reported that horses with PPID had a 5-fold increase in laminitis risk compared to other horses (Wylie et al., 2013). Recommendations for the management of PPID cases with active and/or chronic laminitis are similar to those with ID (Geor and Harris, 2013), and are beyond the scope of this review.

2.4 Age

Although more work is needed in this area, especially for animals with PPID, current evidence suggests that advanced age (>20 years) alone does not significantly affect digestive efficiency in horses (Ralston, 2006, Elzinga et al., 2011). As long as healthy old horses are fed rations that provide calories and nutrients that meet or exceed the recommended amounts for their body size and physiologic status, adjusted for environmental conditions and with adequate anthelminthic administration and dental care, old horses can easily maintain good body condition well into their 20s and even 30s (Ralston and Harris, 2013; Jarvis et al., 2019).

Because most horses with PPID are aged, dental issues need to be considered. If significant dental problems are not present, long fibre is always recommended to cover the DM forage intake requirement (Harris et al., 2017). However, if there are untreatable dental alterations (e.g. missing teeth) or only a small occlusal surface remains (smooth mouth), mastication can become very inefficient (Nicholls and Townsend, 2016). In these scenarios, the necessity of using short fibres (chaff) or fibre pellets (beet pulp or hay pellets) must be contemplated (Ralston and Harris, 2013). If diastemata are present it may be necessary to avoid chaff/chopped fibre as this may promote interdental feed packing. In cases with advanced dental abnormalities, pasture turnout can be a beneficial alternative; however, in cases of PPID with ID, laminitis risk needs to be considered (Ralston and Harris, 2013). Processed fibre nuts/pellets can be soaked with water to help avoid intestinal or oesophageal impactions and increase the water intake. When feeding soaked feeds to older animals, consider that:

- Ideally, soaked feeds should be provided >5 times a day especially if stabled, but such frequent feeding is often impractical. Horses can manage with only 3 feeds a day if pasture is available between meals (even if they quid) or at least over-night.

However, in providing such relatively large infrequent meals, the horse needs to be allowed sufficient time to finish or given a free-choice approach.

- Soaked feeds need to be introduced gradually, starting with a small meal size and then slowly increasing to reach the total fibre/nutrient intake required. Some individuals will not adapt to soaked feeds easily.
- The total amount of fibre-based feed should reach at least 1.5% BW per day on a DM basis (Ralston and Harris, 2013; Harris et al., 2017).
- Low NSC feeds (providing <1g/kg BW/meal) are recommended to help reduce the risk of gastric ulcers, especially with a lack of long fibre.
- Alfalfa pellets can be used to provide a good quality source of protein and leucine, but should not be used as the only source of roughage because it could promote the formation of urinary calculi and/or entheroliths (Cohen et al., 2000; Hassel et al., 2008) or aggravate hepatic or renal dysfunction in aged cases (Ralston and Breuer, 1996). Upper limits for alfalfa provision are not known but as a guide it is recommended to comprise <50% of the ration.
- Soaked feeds should be made up as freshly as is practical (to ensure full soaking but avoiding fermentation starting), and kept as cool as possible (e.g. in a cool feed room) when it is warm outside. On cold days, warm water can be used to encourage appetite, particularly if periodontal disease is present.
- Non-rancid, human grade, calorie dense vegetable oils can be advantageous to add, but they should be introduced slowly, recognising that individuals may prefer certain types of oils or may totally reject the inclusion of any oil. Soaked high-oil low-NSC feed or stabilised calcium-supplemented rice bran/processed flaxseed are alternatives. Up to 1 ml/kg BW can be added to the ration, supported by 1.5 IU vitamin E per ml of added oil (Harris and Schott, 2013).

3- ***Specific nutritional considerations***

3.1 Protein

Since dopamine is derived from amino acids (mainly tyrosine), and a lack of catecholamine precursors could limit dopamine production (Fernstrom and Fernstrom, 2007), it could be suggested that protein/amino acid requirements may be higher in PPID animals. However, specific amino acid or protein requirements have not been investigated. Muscle atrophy is a common clinical sign, and this highlights the importance of protein supply and exercise activity. In a recent study in mature, sedentary horses, supplementation with 0.25g crude protein per kg BW per day on top of a balanced diet stimulated the maximal protein synthesis in skeletal muscle (Loos et al., 2020). Even though animals with PPID were not specifically studied, it suggests that providing extra protein to horses with PPID, as well as aged horses, may be of value.

Threonine and lysine have been identified as major limiting amino acids for horses in general (Graham et al., 1994). Their supplementation (15 and 20 g/day respectively) maintained muscle mass, as evaluated by a subjective muscle mass score, in adult (<10 years old) and aged horses (>20 years old) undertaking a light exercise programme, better than horses provided basal recommended intakes (Graham-Thiers and Kronfeld, 2005). More recently in aged horses, supplementation with threonine, lysine and methionine (40, 30 and 10 mg/kg a day respectively) did not improve whole-body protein metabolism nor nitrogen retention (Latham et al., 2019), although muscle mass scoring was not undertaken. In this later study, basal diet amino acid intakes were not limiting to protein synthesis and the authors concluded that the extra amino acid supplementation may just have been catabolised (Latham et al., 2019).

Supplementation with leucine has been shown to increase total protein synthesis in pigs fed a low protein diet (Yin et al., 2010) as well as in equine satellite cells (DeBoer et al., 2018). In equine satellite cells, the addition of leucine resulted in activation of mTOR translation and increased global protein translation but whole animal studies need to be undertaken.

Practically, alfalfa hay is a forage with good quantity and quality of protein (amino acid profile) for horses (Cuddeford, 2013) and may be especially beneficial when provided as soaked pellets (mash) to equids unable to eat even short fibre as discussed previously. The provision of alfalfa hay (or pellets), may help to prevent loss of muscle mass in older horses (Siciliano, 2002) but no studies have tested this hypothesis.

Especially in horses suffering from muscle wastage, an exercise plan should also be considered as a general management strategy. The training plan should be designed around building and supporting muscle mass, and preventing atrophic processes (Rich, 1989; Hintz, 1995) whilst considering co-morbidities such as laminitis or osteoarthritis. Further work is required to evaluate the most appropriate exercise and the quantity and nature of any additional dietary protein requirements. In the meantime, the authors recommend that horses with PPID are fed at least the recommended levels of protein and essential amino acids (NRC, 2007) for an animal at the same bodyweight but in the next activity level category; i.e. those in light work are fed at least at the level of those in moderate work.

3.2 Vitamins and minerals

3.2.1 General points

Treatment with retinoic acid (the active metabolite of vitamin A) has been shown to be effective in dogs with pituitary adenomas (which similarly to horses could have a melanotropic origin) in reducing both ACTH concentration and adenoma size (Castillo et al., 2006). Nonetheless, no comparable information about the effect of vitamin A supplementation is available for PPID animals. Regarding other vitamins, low plasma vitamin C levels in horses with pituitary gland adenomas have been reported (Ralston et al., 1988). Interestingly, low levels of vitamin B12 have been associated with Cushing's syndrome in humans (Faggiano et al., 2005), and although the pathophysiology is different, a strong negative correlation between PPID and vitamin B12 in horses was recently reported (Siard-Altman et al., 2020a).

Specific recommendations for vitamin supplementation in horses with PPID are not available. Therefore, recommendations per age and activity level are typically suggested (NRC, 2007; Coenen, 2013; Jarvis et al., 2019). When a hay-only diet was provided to adult and aged horses, macro and micronutrient digestibility was decreased compared with hay plus complementary feed (Elzinga et al., 2017), highlighting that horses on a forage-only diet may benefit from vitamin supplementation. Inadequate mineral provision has recently been reported as a typical finding in PPID cases (Kienzle and Bockhorni, 2018), which reiterates the importance of considering dietary evaluation and mineral supplementation. Although there are no specific recommendations for horses with PPID, the authors recommend mineral and vitamin provision at least at the level for horses in light exercise even when not undertaking any structured exercise.

3.2.2 Minerals for insulin dysregulation specifically

Magnesium has been highlighted as potentially playing an important role in managing human diabetic patients to improve their insulin sensitivity (Rodríguez-Morán and Guerrero-Romero, 2003) and hypomagnesemia has been associated with impairment of insulin action. Although there is no evidence of a role for magnesium in PPID, it is important to ensure adequate intake.

Chromium supplementation in humans has been suggested to improve insulin resistance and increase glucose uptake (Hua et al., 2012). In horses, chromium dietary supplementation (dose of 420 µg/kg) increased glucose uptake in yearlings (Ott and Kivipelto, 1999) and enhanced insulin sensitivity in normal adult horses (dose of 2 or 4 mg Cr/day/horse) (Spears et al., 2020). However, in insulin resistant and laminitic horses, supplementation with magnesium and chromium did not result in any changes to resting glucose or insulin concentrations (Chameroy et al., 2011). Given the different results reported, further work would help determine the influence of these nutrients in equine glucose metabolism. Chromium is currently not licenced for use in horses in the UK and EU.

3.3 Antioxidant provision

Antioxidants may be particularly important if oxidative stress is involved in dopaminergic neuron damage (McFarlane, 2011). In horses, four weeks of supplementation with resveratrol (2000 mg/day) beneficially reduced oxidative markers and increased neutrophil antioxidant activity (Adams et al., 2010; Siard et al., 2016). However, in a recent publication (Żak et al., 2020), the profile of oxidative stress markers was no different in horses with PPID compared with similarly-aged healthy horses maintained on an all-forage plus mineral block diet.

Selenium, a major antioxidant, is integrated within various selenoproteins (Kirschvink et al., 2008; Coenen, 2013). Vitamin E is a potent free radical scavenger and antioxidant with reported beneficial effects on immune response in other species (Chandra, 2002). No specific work has been undertaken in horses with PPID, but the authors currently recommend that all horses, and especially older horses, are fed higher intakes of vitamin E (e.g 3-5iu/kg BW [synthetic vitamin E]) and selenium than the basal NRC (2007) recommendations (e.g. basal recommendation of vitamin E 1.6 to 2iu/kg BW depending on activity level) (Harris, 2017).

3.4 Electrolytes

Horses with PPID may suffer from polyuria/polydipsia and excessive sweating (McKenzie, 2007; Robert et al., 2010), which may lead to electrolyte losses. The authors recommend that horses with PPID are provided with constant access to a salt block (suitable for horses and placed in a position that use can be monitored). Additional electrolytes may need to be provided depending on the core ration, activity level, environmental conditions and level of sweat loss (Lindinger, 2008). Clipping the hair coat of horses with PPID to mitigate hyperthermia may also be of value.

3.5 Specific Immune support

Horses with PPID have been suggested to have a higher risk of abscesses and respiratory tract infections (Boujon et al., 1993; McFarlane et al., 2010; McFarlane, 2011), potentially associated with immune system compromise (McFarlane et al., 2010). Impairment of neutrophil function has been reported, potentially contributing to the increase in opportunistic infections in cases with PPID (McFarlane et al., 2015). Additional available vitamin C supplementation would seem sensible as vitamin C has been shown to improve natural lung defences (Deaton et al., 2003), although more research is needed to provide specific recommendations for immune support in PPID cases.

3.6 Inflamm-ageing

The term ‘inflamm-ageing’ (a low-grade systemic inflammatory response associated with ageing) has been used to describe the immune changes observed in older horses and is associated with increased inflammatory cytokine production (Adams et al., 2009). Obesity has also been shown to potentiate this age-associated cytokine dysregulation (Adams et al., 2009), emphasising the importance of weight management in the older horse. Cytokine dysregulation (increased IL-8 and decreased pro-inflammatory cytokines) has also been demonstrated by McFarlane & Holbrook (2008) in PPID horses compared with age matched controls. Recently, acute phase reaction proteins in horses with PPID with and without ID have been investigated (Zak et al., 2020). In PPID non-ID horses, IL-8 was correlated with ACTH concentration, whereas in horse with PPID and ID, serum amyloid A concentration was strongly correlated with ID status. The authors concluded that ID in horses with PPID influences acute phase inflammatory markers. Siard-Altman et al. (2020b) investigated age-related inflammation in PPID horses and concluded that although there was no relationship between PPID and inflamm-ageing, there was a strong negative correlation between levels of vitamin B12 and PPID. This finding suggests it might be beneficial to provide supplementation with vitamin B12, however, more research is required to confirm the dose required and any evidence of efficacy.

Conclusion

Nutritional management is an important part of the holistic management of horses with PPID, in order to optimise health and reduce the risk of clinical sequelae. In tandem with appropriate pharmacological treatment and general management practices, a targeted and personalised dietary plan should be formulated to suit the needs of each case, while prioritising the maintenance of a healthy body condition and the mitigation of ID.

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Figure legends

Figure 1: Flow diagram to show a stepwise approach to the evaluation and dietary management of equids diagnosed with pituitary pars intermedia dysfunction (PPID). Recommended non-structural carbohydrate (NSC) levels in forage: low (<10%), medium (10-18%) and high (>18%). For severely insulin dysregulated animals, NSC intake should be limited to 0.1g NSC/kg BW per meal to achieve a very low insulin response (refer to Section 2.3). Fat refers to vegetable oil/fat, which should be adjusted to target caloric intake (e.g. if weight gain is indicated). Recommendations are a guide only and should be adapted to the individual animal under veterinary supervision.

Abbreviations: BCS = body condition score.

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