

Primary hyperparathyroidism in horses: What can we learn from human medicine?

Philip Johnson¹ and Kile Townsend²

¹University of Missouri

²University of Missouri

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Abstract

Equine primary hyperparathyroidism is rare compared with the condition in human medicine where it is often encountered and represents the most common explanation for hypercalcemia in the outpatient setting. Primary hyperparathyroidism results from a hyperfunctioning parathyroid gland and surgical treatment (parathyroidectomy) is typically curative. Successful surgical removal of a diseased parathyroid gland can be challenging in horses as both normal and hyperfunctioning glands are difficult to localize. Identification of surgical targets using ultrasonography and/or Technetium-99m sestamibi scintigraphy are useful for this purpose in both the human and equine contexts. However, these localization approaches are not always effective. Moreover, not all patients are candidates for general anesthesia and surgery and the costs associated with diagnostic localization and parathyroidectomy may be prohibitive for some owners. This commentary presents information about primary hyperparathyroidism in the event that it is not treated and strives to review aspects of the disease when left untreated from the human medical context.

Clinical Commentary

Primary hyperparathyroidism in horses: What can we learn from human medicine?

P. J. Johnson* and K. S. Townsend

Veterinary Health Center, University of Missouri, Columbia, Missouri, USA

*Corresponding author email: johnsonpj@missouri.edu

The authors of the aforementioned article have described an innovative and helpful method for the identification and surgical excision of an abnormal parathyroid gland that was identified at the thoracic inlet using a combination of pre- and intra-operative Technetium-99m sestamibi scintigraphy but that could not be visualized with ultrasonography (Connard et al., 2023). Whereas the clinical diagnosis of primary hyperparathyroidism (PHPT) in horses is usually straightforward and based on documentation of hypercalcemia, hypophosphatemia, and normal or elevated serum PTH concentrations, the positive identification of the location of an abnormal (hyperfunctioning) parathyroid gland can be very challenging.

Confounding explanations for hypercalcemia that must be routinely considered and ruled out in the human, but not equine, medical context include pseudohypercalcemia and treatment with some pharmaceutical agents. Fictitious total hypercalcemia (pseudohypercalcemia) may be present when hyperalbuminemia is identified because approximately 45% of the calcium in the serum is bound to protein (usually albumin). If hyperalbuminemia is present, the ‘true’ calcium concentration is determined using the following formula: $\text{corrected calcium} = \text{measured calcium} + (40 - \text{measured albumin} \times 0.02)$ [units for calcium concentrations: mmol/l; units for measured albumin concentration: g/l]. A similar correction formula for horses has not been reported and measurement of ionized calcium concentration in serum should allow the diagnostician

to rule out pseudohypercalcemia. Pseudohypercalcemia may also occur in the presence of calcium-binding paraproteins and, following blood collection, through release of intracellular calcium by platelets in thrombocytopenic states. Treatment with lithium may elevate both circulating plasma parathyroid hormone and calcium concentrations. Hypercalcemia may also result from treatment with thiazide diuretics (such as hydrochlorothiazide), which enhance renal calcium reabsorption. When applicable, reassessment of calcium and parathyroid hormone levels should be undertaken at least three months following discontinuation of these medications (Al-Azem and Khan 2011; Dandurand et al., 2021).

In human medicine, familial hypocalciuric hypercalcemia (FHH) must also be considered in the differential diagnosis of hypercalcemia, particularly in younger patients (<20 years of age); acquired PHPT is more common in older human and equine individuals. Although not, to our knowledge, described in horses, FHH is an inherited condition (autosomal dominant transmission) in which the calcium-sensing receptor is inactivated because of a gene mutation. Elevated levels of both serum calcium and parathyroid hormone (or inappropriately normal parathyroid hormone levels in the face of hypercalcemia) are also identified in FHH, thus mimicking PHPT. The FHH mutation also affects the kidneys; hypocalciuria results from increased renal tubular calcium resorption. Diagnosis of FHH is additionally based on demonstration of a very low urinary clearance ratio of calcium to creatinine and genetic studies. Although it must be considered as an explanation for incidental hypercalcemia in asymptomatic (human) patients, identified on routine screening, FHH is an otherwise benign condition that does not require surgical treatment (parathyroidectomy) (Al-Azem and Khan 2011; Carrala et al., 2021).

It has been suggested that, when PHPT is identified in horses with comorbid thyroid gland neoplasia, pheochromocytoma, and pituitary *pars intermedia* dysfunction, it may be similar to the situation in human medicine in which PHPT is sometimes identified as a component of multi-endocrine neoplasia (MEN) syndromes. Multiple endocrine neoplasia is defined by simultaneous neoplasia and hyperplasia of multiple endocrine tissues and has an inherited basis in humans (Hoff et al., 2000; Miedlich et al., 2002; Bringham et al., 2008). In one horse with PHPT the surgical removal of an abnormal parathyroid gland failed to resolve hypercalcemia and elevated serum PTH levels. In that case, it was suggested that there might have been other unidentified parathyroid tumors, or that the horse was affected by a MEN-like syndrome (Villagrán et al., 2014). A multi-endocrine neoplasia syndrome has also been reported to (rarely) cause hypercalcemia in horses (De Cock and MacLachlan 1999; Germann et al., 2006). Both normal and abnormal parathyroid glands are difficult to locate in horses (including at postmortem examination). Type 2a MEN (Sipple's syndrome), characterized by the co-existence of medullary thyroid carcinoma, hyperparathyroidism, and pheochromocytoma in the same individual, should be considered with this finding in horses, even if an affected parathyroid gland cannot be located (Luethy et al., 2016).

Similar to the situation in other domestic animal species, horses are invested by two pairs of parathyroid glands; the anatomical location of the caudal pair of glands is especially variable being located anywhere along the length of the carotid arteries from the cranial cervical region to the thymus (Wong et al., 2004; Tomlinson et al., 2014). Technetium-99m sestimibi parathyroid scintigraphy is a nuclear medicine procedure that is performed to localize parathyroid adenoma (hyperfunctioning parathyroid glands absorb the radionuclide faster than normal glands) (Gotway et al., 2002). As with the case described here, overactive parathyroid glands can sometimes be identified using sestimibi scanning; radionuclide uptake by abnormal parathyroid gland cells correlates with the number and activity of their mitochondria. Normal parathyroid glands in the same patient are not identified by sestimibi uptake because they are inhibited through normal negative feedback mechanisms. Sensitivity of sestimibi scanning for the purpose of abnormal parathyroid gland localization has been improved in human medicine through the introduction of single-photon emission computed tomography (SPECT) (Neumann et al., 2008). Obviously, this technology is not currently available in the equine diagnostic setting. Even using the sophisticated imaging technology that is available to human medical diagnosticians, false negative outcomes are reported for between 5-38% of human PHPT cases with sestimibi scanning. Numerous different factors that are related to the absence of uptake in sestimibi scintigraphy in PHPT patients have included young age, female gender, ectopic or upper location, high body mass index, low oxyphilic cell content, small adenoma size (<500 mg), patient motion, ectopy, number

of adenomata, and co-existence with nodular thyroid gland disease (Nichols et al., 2008; Greenspan et al., 2012; Carrala et al., 2021).

Although the sensitivity of Tc-99m sestimibi nuclear medicine scans for detecting parathyroid adenomas in horses is unknown, it has been reported to be approximately 90% in humans (Hillyar et al., 2022) and 17% in dogs (Matwichuk et al., 2000). In addition to the report in this issue (Connard et al., 2023), Tc-99m sestimibi scintigraphic scanning has been reported to be effective in 13 of 16 (81%) previously published cases (Wong et al., 2004; Tomlinson et al., 2014; Cottle et al., 2016; Gorenberg et al., 2020; Colmer et al., 2022).

Three quarters of human patients are asymptomatic and do not exhibit symptoms that are explained by PHPT, the clinical course of which has been described as being rather benign (Miedlich et al., 2002). In contrast to the situation in equine medicine in which it is regarded as rare, primary PHPT is a much more common endocrine condition in people, affecting approximately 0.86% of the USA population (Kahn et al., 2017; Dandurand et al., 2021). It is the most common explanation for hypercalcemia in the outpatient setting (Dandurand et al., 2021). Hypercalcemia associated with PHPT results from the influence of elevated circulating PTH levels causing increased renal tubular calcium reabsorption, enhanced bone resorption through stimulated osteoclasts, and increased renal $1,25(\text{OH})_2\text{D}_3$ synthesis (which stimulates both calcium and phosphate absorption in the intestine) (Dandurand et al., 2021).

In the past, PHPT was recognized clinically when affected individuals developed complications of osteopenia and bone fragility or evidence of renal disease (Minisola et al., 2018). In more recent years, the inclusion of plasma calcium concentration as a component of routine health assessments in Western society has led to earlier recognition of subclinical PHPT. Asymptomatic PHPT is commonly encountered in people with mild disease and does not necessarily necessitate surgical treatment. In these cases, the patients are monitored and treated conservatively. Early clinical signs of PHPT in equine patients are often very nonspecific and include lethargy, loss of bodily condition, reduced appetite or anorexia, ill-defined, shifting lameness, and stiffness (Tomlinson et al., 2014; Villagrán et al., 2014; Schwarz et al., 2019; Darby et al., 2020; Gorenberg et al., 2020). A number of considerations from the human medical context that may be relevant to some of the signs seen in equine PHPT include the fact that bone pain is described in people with high calcium concentrations (Miedlich et al., 2002; Khosla 2014). Additionally people affected with hypercalcemia commonly report depression, headache, fatigue, exhaustion, and cognitive dysfunction (Miedlich et al., 2002; Shane and Irani 2006). Other self-reported symptoms in the human context include weakness, constipation forgetfulness, and lack of interest (Brown and Macleod 2001; Hall 2011).

There has been increasing recognition of the fact that mild/asymptomatic PHPT in people may be present for many years before specific clinical problems arise, affecting principally skeletal structures and the kidneys. Hyperparathyroidism is often discovered incidentally because most affected equids do not exhibit clinical signs over the course of several years (Roussel and Thatcher 1987). If surgical treatment (parathyroidectomy) is not undertaken (or unsuccessful), the clinical course for (human) patients with mild or asymptomatic PHPT appears to be quite stable. Circulating plasma calcium and parathyroid hormone levels and bone density may remain stable for up to 10 years (Bilezikian et al., 2009), following which time bone density may begin to decrease (Al-Azem and Khan 2011). This observation is important to consider from the equine perspective because PHPT may have been present in affected horses for at least several years with absence of radiographic or histopathological evidence of osteopenia (stimulated osteoclasts) (Schwarz et al., 2019; Connard et al., 2023).

Human patients with asymptomatic mild primary hyperparathyroidism that are not surgical candidates are monitored and treated with calcimimetic agents when osteoporosis or declining bone mineral density are identified (Dandurand et al., 2021). Moreover, pharmacological treatment of PHPT is also advocated for the management of inherited (familial) forms of hyperparathyroidism, following surgical failure, and for those patients who refuse surgery.

Although (human) patients with mild asymptomatic PHPT may be medically managed for some time without

resort to parathyroidectomy, the onset of renal dysfunction (with diminished glomerular filtration rates) and osteoporosis (based on monitored densitometric criteria) will eventually warrant consideration of parathyroidectomy because of the increased risk of pathological (fragility) fracture. Poor bone mineral density (BMD), as may arise in cases of PHPT is associated with elevated risk of fracture. Therefore, the assessment of BMD is routinely undertaken for human patients using, for example, dual energy X-ray absorptiometry (DEXA). In addition to PHPT, other conditions that warrant DEXA scanning in people include age (women after 65 years and men after 70 years of age), eating disorders, employment of androgen deprivation treatments for management of prostate cancer, long term glucocorticoid treatment, and other bone conditions. Although assessment of BMD in horses is somewhat in its infancy, there have been some post-mortem studies (dissected bones) employing DEXA that have demonstrated correlation between BMD and the force needed to break the third metacarpal *in vitro* (Junge et al., 2011; Tóth et al., 2014). Assessment of BMD has also been reported for living horses using a radiographic bone aluminium equivalence method (Nielsen et al., 2017; Maher et al., 2020). Deprivation of osteoid from bones (osteopenia) as a result of osteoclast-mediated bone resorption leads to bone fragility and increased risk for fracture.

Historically, diagnosis of late stage PHPT was commonly based on the identification of characteristic radiographic changes that include salt-and-pepper skull appearance, distal clavicle tapering, subperiosteal bone resorption, bone cysts and brown tumors (collectively referred to as osteitis fibrosa cystica) (Dandurand et al., 2021). Encounters with pathological fracture and osteitis fibrosa cystica are now much less commonly reported in developed countries because earlier diagnosis of PHPT is facilitated through routine blood testing during annual medical examinations. Whereas clinical evidence of bone fragility and radiographic osteopenia have been reported in some PHPT-affected horses, these abnormalities are not evident in all cases. Results from a 15-year observational study that evaluated 57 human patients with asymptomatic PHPT showed that worsening hypercalcemia did not occur until year 13 and that other measured outcomes (including serum PTH levels) were stable throughout (Rubin et al., 2008). Moreover, whereas vertebral BMD remained unchanged there was significant bone loss in the distal radius by year 8. These observations point to the fact that, in many (human) cases, clinically important osteoid depletion occurs over a long period of time and that progressive loss of BMD differs between bones at different locations. Using DEXA scanning, it has been shown that reduction in BMD is most evident in the radius (mostly cortical bone) and much less evident in lumbar vertebrae (rich in trabecular bone) (Syed and Khan 2000; Miller and Bilezikian 2002).

The extent to which PTH-induced loss of BMD affects different bones in the equine condition has not been much explored and might be examined prospectively when veterinarians encounter new PHPT cases in the future. Of specific interest and reported more commonly in horses affected with secondary hyperparathyroidism (SHPT) (from nutritional etiologies), horses under the influence of elevated PTH may develop *osteodystrophia fibrosa* of the facial bones in addition to osteopenia at other skeletal locations. In their recent retrospective study of 17 PHPT-affected horses, Gorenberg et al (2019) reported that skull and limb radiography (or both) was undertaken in 8 horses to screen for bony changes. Abnormalities that were identified in those cases included osteopenia of the limbs or skull (5 cases), dystrophic mineralisation (2 cases), laminitic changes of unknown cause (1 case) and focal loss of the lamina dura of the first molars (1 case). Radiographic evidence of diminished BMD is insensitive in that it requires at least 30% loss (Toribio 2011). When successful, surgical treatment of people affected with PHPT (parathyroidectomy) provides skeletal protection and reverses the risk of pathological fractures associated with increased bone fragility (Dandurand et al., 2021).

In the human condition, PHPT is also associated with the development of kidney stones, nephrocalcinosis, and renal insufficiency (Dandurand et al., 2021). Kidney stones are identified more frequently in asymptomatic PHPT patients than in the unaffected population; stone formers are more likely to be hypercalciuric than non-stone formers (Lila et al., 2012). The risk of further stone formation is lowered following parathyroidectomy but remains higher than that seen in the euparathyroid population.

Even though PTH stimulates renal calcium resorption, the primary determinant of the amount of calcium excreted into the urine per day is the ionized calcium concentration in plasma. In PHPT, the daily quantity of calcium excreted in the urine is increased in spite of high circulating PTH levels, because hyperparathyroidism

results in hypercalcemia, thus increasing the urinary calcium concentration (hypercalciuria). Nephroliths are often one of the first signs of PHPT in people, especially when it is considered that hypercalciuria is accompanied by enhanced urinary phosphate excretion (through the action of increased PTH); calcium and phosphate concentrations in the tubular fluid may exceed their solubility product and form precipitate as calcium phosphate stones.

Renal functional impairment is also identified in approximately 17% of asymptomatic human PHPT patients and is associated with the severity and duration of hypercalcemia (Tassone et al., 2015). When identified, impaired renal function leads to recommendation for surgical intervention. Parathyroidectomy prevents worsening renal dysfunction in PHPT cases. Nephrocalcinosis is identified via CT in approximately 10% of asymptomatic PHPT patients. Risk factors for nephrocalcinosis have not been identified in these PHPT cases and it does not respond to parathyroidectomy.

Clinically evident renal complications of PHPT are not reported (hitherto) in horses but acute kidney injury may arise following parathyroidectomy (Gorenberg et al., 2020). The reason for postoperative azotemia in these circumstances is unknown, but all of those patients responded favorably to fluid therapy. Histopathological changes are sometimes reported in the kidneys of PHPT-affected horses post-mortem and have included deposition of calcium salts in the form of granules in the lumen and lining of collecting tubules and in adjacent interstitial tissue (Schwarz et al., 2019). Close attention to the kidneys and renal function in horses affected with PHPT is clearly warranted.

Unless an abnormal hyperfunctioning parathyroid gland can be identified and its location defined, surgical removal (parathyroidectomy) or chemical ablation with ethanol may not be possible (Colmer et al., 2022). Whereas surgical treatment (parathyroidectomy) is recommended and curative for patients with both clinical disease and asymptomatic disease in the absence of comorbidities, medical treatment can be employed. Medical treatments are used in cases in which PHPT-affected individuals are not suitable candidates for general anesthesia or surgery, surgical treatment is declined, or for those cases in which previous surgical treatment has failed. Medical treatment may be explored further for equine PHPT patients because pre-operative localization of an abnormal parathyroid gland (using sestimibi scintigraphy and ultrasonography) may be unsuccessful, and the costs associated with scintigraphy and surgical treatment may be prohibitive.

Medical management of PHPT was partially successful in only 2 of 7 equids in which it was attempted. (Gorenberg et al., 2020) Although dietary restriction of calcium was undertaken in 5/7 cases in that retrospective study, it should be noted that calcium restriction is not recommended in human PHPT patients because it may drive further PTH release and worsen bone resorption (Marcocci et al., 2014; Dandurand et al., 2021). Whereas surgical treatment for PHPT in dogs is also often recommended, the short-term management of severe hypercalcemia may include administration of IV fluids (for diuresis), bisphosphonates and glucocorticoids, especially if either or both azotemia or a high plasma calcium-phosphorus product are identified (Schaefer and Goldstein 2009).

Bisphosphonates, acting through inhibition of osteoid degradation by osteoclasts, are the most commonly prescribed group of drugs for the treatment of osteoporosis in human medicine. These drugs are also used for the medical management of human PHPT in nonsurgical cases. Modest increases in BMD have been documented when bisphosphonates are used for mild PHPT in people (Dandurand et al., 2021). Tiludronate was administered to one horse with PHPT in which a mild but incomplete improvement in hypercalcemia status was reported (Gorenberg et al., 2020). In another report, tiludronate ameliorated clinical signs (but not laboratory abnormalities) associated with nutritional secondary hyperparathyroidism (Lacitignola et al., 2018).

The calcimimetic agent, cinacalcet, acts through allosteric activation of calcium-sensing receptors at the surface of chief cells in the parathyroid glands where it increases their sensitivity, reducing PTH secretion and reducing plasma calcium levels (Kahn et al., 2015; Kahn et al., 2017). Cinacalcet is primarily indicated for the management of SHPT in people affected with chronic renal disease. It is also approved for the management of PHPT in people for whom surgery is not indicated or possible and in whom surgical treatment

has not been successful. Although cinacalcet treatment for PHPT leads to improvements in both PTH and plasma calcium levels, it does not afford skeletal protection. However, treatment using a combination of cinacalcet and a bisphosphonate improves skeletal health. To our knowledge, treatment of horses affected with hyperparathyroidism using cinacalcet has not been reported at this time.

The authors noted that the diagnosis of PHPT had been appropriately based on identification of hypercalcemia and an elevated serum PTH level. Two other important explanations for hypercalcemia in the equine species, chronic renal failure and hypercalcemia of malignancy, were further ruled out based on normal plasma creatinine and thymidine kinase-1 levels in blood, respectively. Paraneoplastic hypercalcemia has been previously recognized in horses affected with lymphoma, multiple myeloma, ameloblastoma, mesenchymal ovarian cancer, squamous cell carcinoma, gastric carcinoma, and adrenocortical carcinoma (Barton et al., 2004; Axiak and Johnson 2012). Demonstration of elevated levels of circulating cancer biomarkers for the purpose of affirming or ruling out presence of neoplasia would represent a helpful advance in cancer diagnosis for all species (Tivey et al., 2020). It is unlikely that a solitary, ideal biomarker will apply in all cases because the importance of various biomarkers depends on the type of cancer. Moreover, the extent to which cancer biomarkers have been investigated in horses is very limited. Elevated levels of PTH-related peptide (PTH-rP) were reported in one horse affected with multiple myeloma (Barton et al., 2004). Although elevated serum thymidine kinase-1 (TK1) levels have been proposed as useful diagnostic indicators of lymphoma in horses (Larsdotter et al., 2015), later studies yielded conflicting results (Moore et al., 2021; Wang et al., 2021). Although the authors concluded that a paraneoplastic explanation for hypercalcemia could be ruled out based on a normal TK1 level in their patient, caution in that regard is recommended until better cancer biomarkers with improved positive and negative predictive values have been evaluated and validated for both equine and human medicine.

Although this commentary has been centered on the subject of PHPT, the fact that horses also develop secondary hyperparathyroidism (SHPT) should not be overlooked. The equine veterinary literature contains many excellent and well-illustrated references to SHPT resulting from historical and contemporary nutritional factors. For review of SHPT in horses, readers are encouraged to review a recent paper in which SHPT resulted from the ingestion of soursob weeds (Herbert and Dittmer 2017). Whereas SHPT is most commonly recognized in the context of renal disease in people, this phenomenon (renal SHPT) does not appear to occur in horses. In almost all cases, equine SHPT can be traced back to the ingestion of nutritional factors that interfere with the oral bioavailability of calcium from the diet (excessive bran, dietary feeding errors, plants that contain high levels of oxalate, etc).

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