

Do Thyroid Disorders in Horses Really Exist?

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Keypoints

- Hypothyroidism is not common despite its widespread diagnosis.
- Congenital or juvenile hypothyroidism is seen in western Canada where dietary iodine levels may be insufficient, resulting in goiter and limb deformities.
- Experimental hypothyroidism results in profound bradycardia, poor response to cardiac β -receptor stimulation, and exercise intolerance. These signs are reversible with exogenous thyroid hormone supplementation.
- Aged horses frequently develop benign thyroid adenomas resulting in thyroid enlargement.

Introduction

Confirmed cases of hypothyroidism in the horse are rare, yet hypothyroidism is routinely implicated as the underlying cause of a litany of medical problems in horses. Market sales for equine thyroid supplements in the United States were reportedly over \$1 million annually in the mid-1990s.^a The true prevalence of the condition is unknown. Many euthyroid horses have undoubtedly been mis-diagnosed as hypothyroid due to the difficulty in accurately confirming the diagnosis. The ease of treatment and the widely accepted potential benefits most likely have encouraged the trend of over-diagnosis of hypothyroidism.

Thyroid Physiology

Thyroid hormone production. The thyroid gland concentrates iodine absorbed from the stomach and upper small intestine as iodide ions.¹ Inorganic iodide in the thyroid gland reacts with tyrosine to form monoiodotyrosine and diiodotyrosine. These couple to form triiodotyrosine (T3) and thyroxine (tetraiodothyronine or T4). Glandular cells form thyroglobulin which attaches to thyroxine to form follicular colloid which acts as an extravascular storage reservoir for thyroid hormone. The release of thyroid hormone from the thyroid gland is directly controlled by thyroid-stimulating hormone (TSH or thyrotropin) released from the hypothalamus. The thyroid hormone freed from the thyroid gland immediately becomes bound to thyroxine-binding globulin, pre-albumin, and albumin. Less than 1% of thyroxine is free or unbound. Only the free state of T3 and T4 are physiologically active. Most of the plasma inorganic iodide not taken up by the thyroid gland is excreted via the urine and the feces.

Thyroid hormone action. Tetraiodothyronine is transported intracellularly by both active and passive diffusion. Once inside the cell, T₄ is deiodinated to form T₃.² Triiodothyronine then interacts with its nuclear receptor and induces transcription, resulting in the production of mRNA, which leaves the nucleus and is translated on ribosomes to specific proteins. These proteins and enzymes are responsible for the diverse metabolic effects of thyroid hormones. Triiodothyronine is the most active of the thyroid hormones and is vital to every major organ system.³ It stimulates cellular oxygen consumption and basal metabolism. It is responsible for the promotion of growth and maturation of cells. It stimulates heart rate, cardiac output, and blood flow. Triiodothyronine also plays an important role in lipid and carbohydrate metabolism.

Types of thyroid abnormalities. Equine abattoir surveys have documented varying rates of thyroid abnormalities. In one 1931 study of 100 equine thyroid glands, 34 were normal, 20 were hyperplastic, 9 were termed colloid goiters, and 37 were adenomatous.⁷ No adenoma was found in horses less than 10 years of age. Investigators in western Canada in 1934 found a much higher incidence of goiters in their survey of 60 adult horses. They reported 58.3% normal, 13.3% hyperplastic, and 28.3% colloid goiters. In a third histological study of equine thyroids, 27 of 59 (45.8%) were classified as normal, 20 (33.9%) were hyperplastic, 4 (6.8%) were colloid, and 1 (1.7%) was adenomatous. It remains unclear from this latter study how the remaining 7 thyroids were classified.

There are no reports of histologic studies on non-neoplastic thyroid glands of horses affected with hypothyroidism except for Waldron-Mease in 1979, who biopsied the thyroid gland of one horse affected by recurring myopathy and suspected of having secondary hypothyroidism. Histological findings were of “densely staining follicles with flattened epithelium and little evidence of vacuolization.” The histological report suggested secondary hypothyroidism by pituitary suppression.

Diagnosis of hypothyroidism

A diagnosis of hypothyroidism in the horse is based on clinical signs, the presence of enlarged thyroid glands (unilateral enlargement in neoplasia, bilateral in dietary-induced goiter), and resting total and free plasma T₃ and T₄ concentrations. Stimulation tests with TSH or TRH provide a definitive assessment of thyroid function but these are currently unavailable as approved products for horses. Routine [TSH] assays may provide more information in diagnosing hypothyroidism than can currently be obtained from resting serum [T₃] and [T₄] determinations. In some cases, response to thyroid hormone supplementation may be necessary as an adjunct in diagnosis.



Factors affecting plasma T3 and T4 concentrations in the horse

The extent of plasma protein-binding of thyroid hormone is affected by many factors, including drugs, starvation, non-thyroidal sickness, endogenous hormones, and pregnancy.² Thyroxine concentrations are increased by estrogen, insulin, and pregnancy,² and decreased by corticosteroids (i.e., Cushing's disease from a pituitary adenoma), phenytoin, salicylates, anabolic steroids, barbiturates, trimethoprim-sulfa, phenylbutazone and non-thyroidal illness.

Clinical manifestations of thyroid disease in horses

Goiter. Goiter is defined as any nonmalignant enlargement of the thyroid gland. It may be accompanied by either hypothyroidism, euthyroidism, or hyperthyroidism. The enlargement may be due to an increase in the amount of thyroid tissue (hyperplasia) or due to an increase in the amount of colloid causing distention of thyroid acini. Inflammatory proliferation occurs less commonly. The pathogenesis includes iodine-deficient diets, goitrogenic compounds that interfere with thyroxinogenesis, dietary iodine excess, and genetic enzyme defects in the biosynthesis of thyroid hormones.¹⁶ All of these factors result in inadequate thyroxine synthesis and decreased blood concentrations of T3 and T4. The lowered thyroid hormone concentrations are detected by the hypothalamus and pituitary and result in an increase in the secretion of thyrotropin with the resulting hypertrophy and hyperplasia of follicular cells.

Fetal, congenital, or juvenile hypothyroidism has been reported in foals born to dams maintained on diets containing inadequate or excessive concentrations of iodine. There have been no reports of congenital enzyme deficiencies in the horse, but they have been reported in Sanaan goats.

Certain plants are known to be goitrogenic when consumed. Included in these are soybeans and members of the Brassica family (cabbage, rape, kale, and turnips). Heating or processing destroys the goitrogenic substances in these plants. Goitrogenic substances have been transmitted through the milk (glucosinolates). A major effect of the hydrolysis products of glucosinolates is inhibition of the thyroid gland. As antithyroid agents, they have four general effects: (1) they may interfere with iodine uptake by the thyroid gland (e.g., thiocyanate), (2) interference with tyrosine iodination, (3) suppression of thyroxine secretion, or (4) function as a metabolic antagonist to thyroxine in the tissues.

The antithyroid effect of excess iodine is not well understood. In 1986, Baker and Lindsey postulated two mechanisms for toxicosis: (1) excess iodine inhibits thyroid hormone synthesis by inhibiting conversion of moniodotyrosine to diiodotyrosine, and (2) excess iodine prevents the release of thyroid hormone from the thyroid gland.¹⁸

Lowered serum [T3] and histological thyroid gland changes have been reported in foals born to mares which grazed endophyte-infested fescue pastures while pregnant.

Neonatal/pediatric horse effects of hypothyroidism. Hypothyroidism in the foal is usually congenital and has been associated with musculoskeletal defects. Doige and McLaughlin investigated hypothyroidism in 14 unrelated foals. These foals were weak at birth and required assistance to suckle. Their abnormalities included ruptured common digital extensor tendons, forelimb contracture, mandibular prognathism, skeletal hypoplasia, poorly ossified or malformed carpal and tarsal bones leading to severe angular limb deformities. Ten of the 14 foals had abnormally low serum total T3 and/or T4 concentrations, suggesting hypothyroidism. Response to TSH stimulation performed in only two foals was poor. Six of the 7 foals that were necropsied had histological evidence of thyroid hyperplasia. The thyroid follicles were small, crowded, irregularly-shaped, and contained very little colloid. This lesion is indicative of chronic stimulation by TSH in response to low circulating concentrations of thyroid hormone. The dams of these foals were clinically normal. Reviews of the dams' diets during pregnancy revealed no obvious dietary deficiencies. The authors speculated that iodine deficiency was the culprit. Subsequent reports have further verified that forage from this area of western Canada is frequently deficient in iodine, resulting in iodine deficiency in many foals born to mares not supplemented with extra dietary iodine.^{19,22} Interestingly, much earlier reports (1934) from investigators in western Canada found a much higher incidence of goiters in their survey of 60 adult horses. They reported 58.3% normal thyroids, 13.3% hyperplastic, and 28.3% colloid goiters.

The same investigators also thyroidectomized neonatal foals to monitor ossification of the carpal and tarsal bones.²³ They found that this thyroidectomized group of foals had a reduced rate of ossification, especially of the second and fourth carpal bones. However, the decrease in the rate of ossification in the surgically thyroidectomized foals was of a lesser degree than that in foals with congenital hyperplastic goiter which had their central and third tarsal bones most severely affected.

In another case report by Vivrette and co-workers, hypothyroidism was diagnosed in a five-month old Thoroughbred colt. Skeletal lesions included delayed appearance of ossification centers and delayed development of bone in cartilage models, delayed closure of epiphyseal plate, transverse trabeculation in metaphysis, osteochondrosis dissecans, and subchondral bone cysts. Clinically, the colt was stunted and listless, had a subnormal rectal temperature, and a coarse hair coat, anemia, and lipemia. The resting total serum T3 and T4 concentrations were low. There was no response to the TSH stimulation test. The colt was euthanatized and there was no mention of treatment with thyroid hormone.

Murray described a case of hypothyroidism and respiratory insufficiency in a neonatal foal. Both thyroid glands were enlarged upon presentation. A TRH stimulation test was abnormal in that there was no increase over baseline in free and total plasma/serum T4 concentrations. There was a slight increase over baseline in free and total plasma/serum T3 concentrations. There was some subjective improvement in the clinical signs with levothyroxine supplementation. The foal died suddenly on day 8 of hospitalization. The necropsy findings included large thyroid glands with moderate lymphoid depletion. As thyroid hormones are necessary for maturation of the lung epithelium in many species, it is possible that the clinical signs of respiratory disease were caused by the lack of normal thyroid function.

Irvine described hypothyroidism in foals as occurring as two different entities because of the separate actions of thyroid hormones in regulation of metabolic rate and cell differentiation. The hypometabolic state which results in inadequate thermogenesis and lethargy occurs concurrently with a period when thyroid hormone secretion is inadequate. By contrast, the developmental lesions are often observed during the periods when plasma thyroid hormone concentration are normal. During the development of most tissues there is a period during which deprivation of thyroid hormone leads to defects which may appear weeks later when the thyroid hormone concentrations have returned to normal. In the foal, the critical period for some developmental processes (e.g., myelination) is before birth so it is difficult to confirm a prenatal hypothyroid state as the cause of neonatal neuromuscular incompetence. Postnatal developmental lesions of the epiphyses or ossification centers, for example, may manifest themselves weeks after the period in which hypothyroidism existed.

Baker and Lindsey also described a case of goiter in a foal. This foal exhibited fetlock hyperextension and a weak suckle reflex. There were no osseous abnormalities detected. The foal had a unilaterally-enlarged mass on the upper third of the neck. The serum total T4, serum T3 uptake, free T4 index, and serum TSH concentrations were normal compared to age-matched controls. The mass was removed but no long term follow-up was available. They hypothesized that the cause for the goiter was iodine deficiency, but there was no information provided about the dam's diet during pregnancy. Their description of a unilateral goiter is interesting but seems unlikely to be due to dietary insufficiency since the definition of goiter is bilateral thyroid hyperplasia.

Adult horse sedentary effects of hypothyroidism. Actual reported cases of adult horses afflicted with primary hypothyroidism are rare. There have been limited reports of thyroid carcinomas with and without associated exercise intolerance. There has also been a case of thyroid adenoma reported in the literature in which a surgical thyroidectomy for cosmetic reasons. The horse in question had a non-painful unilateral enlargement on the neck caudal to the ramus of the mandible. It had normal resting total serum T3 and T4 concentrations and responded to a TSH test with the expected two-fold increase over baseline. Surgical excision was curative.

There is one case report of alopecia associated with hypothyroidism in a horse. The authors described a horse with normal serum [TT4] but low [TT3]. They postulated a poor conversion of T4 to T3 resulting in functional hypothyroidism. They did not perform a TSH test but treated the horse with triiodothyronine (1 mg/kg PO Cytobin tablets, 120 µg each) for 6 weeks at which point the hair coat had started to return to normal.

There have also been reports associating laminitis with hypothyroidism. In a study by Hood and Hightower, acute laminitis was induced using a carbohydrate overload model. Serum T3 and T4 concentrations were depressed during the 48 hours before the onset of lameness following the induction of acute laminitis. Horses with chronic laminitis had significantly elevated serum T3 concentrations, but serum T4 concentrations were not statistically different from controls. In addition, the TSH responses were similar for the 3 groups. The authors postulated that the elevated T3 concentrations reflected the pathogenesis of laminitis rather than reflecting thyroid

dysfunction (e.g., sick thyroid syndrome). They also commented on the inappropriate empirical treatment of laminitic horses with thyroid replacement unless a true thyroid dysfunction can be demonstrated.

Lowe and Kallfelz surgically thyroidectomized horses ranging in age from 17-20 months and then observed their growth and metabolism over 67 subsequent weeks. The clinical signs described included: non-painful eyelid swelling; lethargy; docile temperaments; no increase in height but maintenance of normal body weight; low grade anemia; elevated serum cholesterol concentrations; and a decrease in the rate of skeletal growth and maturity. They also felt that the thyroidectomized horses were more sensitive to cold weather, shed their winter hairs late, and had dull coarse hair coats. The horses had edema of the rear limbs and decreased rectal temperatures. Physeal plate closure time was delayed as was the eruption of incisor teeth. Thyroprotein supplementation resulted in a rapid and dramatic reversal of some of the signs of hypothyroidism “such as rectal temperatures and rear leg edema”. The dose of thyroprotein was adjusted using frequent T4 measurements to obtain normal total T4 concentrations. Discontinuance of the thyroprotein supplementation resulted in a return of hypothyroidism but not to the degree seen prior to the supplementation (although the T4 values fell below the lower limits of the assay).

Lowe and coworkers subsequently thyroidectomized 6 young horses and followed them for a total of 67 weeks to assess the long term effects of surgical hypothyroidism. When compared to age-matched normal cohorts, the thyroidectomized foals failed to grow in height, were sensitive to cold, shed their winter coats later, and had dull coarse hair coats. They were also judged to be more docile and lethargic. They had edema of the hind limbs similar to the myxedema seen in humans with hypothyroidism.⁸⁵ Rectal temperature and heart rate were decreased and serum cholesterol was increased. Physeal plate closure was delayed as was eruption of incisor teeth. Thyroprotein supplementation resulted in dramatic and rapid reversal of the clinical signs, with increased feed consumption, heart rate, rectal temperature, and serum T4 concentrations.

Recent work from Frank and colleagues has shown dramatic effects of thyroidectomy on fat metabolism in horses. Mean plasma very low-density lipoprotein (VLDL) and low-density (LDL) lipoprotein concentrations increased significantly after surgical thyroidectomy. Serum concentrations of triglycerides and total cholesterol increased and serum non-esterified fatty acid concentrations decreased within 4 weeks of surgery. Their conclusion was that examination of blood lipid concentrations might be useful indicators in horses of naturally-occurring hypothyroidism.

Despite the fact that hypothyroidism in other species has been shown to have profound effects on the cardiovascular system, the hemodynamic effects of hypothyroidism have never been investigated adequately in horses until recently. Using six aged Quarter Horse mares with extensive treadmill experience, we recently showed in our laboratory that thyroidectomy resulted in a down-regulation in activity of cardiac β -receptors, resulting in a remarkable resting bradycardia (heart rate <20/min) and an inability to respond to exogenous β -stimulation by isoproterenol infusion (Vischer, Foreman, *et al.*: Hemodynamic effects of thyroidectomy in sedentary horses. *Am J Vet Res* 1999;60:14-21). Responses to stimulation of α -receptors by phenylephrine were not affected by thyroidectomy. Interestingly, the horses neither gained nor

lost weight when hypothyroid, including for a several month period after the study concluded when they were housed outside and fed hay only. Dietary supplementation with exogenous thyroid hormone resulted in reversal of many of the adverse effects of thyroidectomy, including reversal of the down-regulation of β -receptor responsiveness.

Adult horse exercise effects of hypothyroidism. There have been three published reports of thyroid adenocarcinomas in horses with or without associated exercise intolerance. Surgical removal of the thyroid carcinoma and supplementation with exogenous thyroid hormone allowed one horse to return to normal exercise levels.

Waldron-Mease reported on an association of hypothyroidism and exertional myopathy in Standardbred and Thoroughbred racehorses. The horses presented with poor performance records, dullness and stiff gait. The condition was diagnosed as secondary hypothyroidism based on normal TSH responses (n=5 of 5 horses tested) but low basal serum TT4 concentrations (n=6). Improvement was reported following thyroid replacement therapy. It is possible that these horses were only suffering from sick thyroid syndrome which artificially lowered their thyroid hormone concentration rather than actually suffering from pituitary dysfunction as they did not exhibit other signs compatible with pituitary disease.

Conversely, recent work showed no abnormalities in thyroid function in Quarter Horses and Thoroughbreds with histories and documented clinical problems with exertional myopathy.

Until recently, the supposed effects of thyroid function on exercise have not been adequately investigated in the horse prospectively through a study with complete surgical thyroidectomy. When we exercised our thyroidectomized mares, they were exercise intolerant, again primarily due to an inability to generate sufficient heart rate to achieve relatively-easy work rates on the high speed treadmill (Vischer, Foreman, *et al.*: *J Vet Intern Med* 1996;10:151). Dietary supplementation with exogenous thyroid hormone resulted in reversal of the exercise intolerance. This study represents the first proof of the hemodynamic and exercise-intolerance effects of hypothyroidism in athletic horses, and also debunks the commonly-held belief that hypothyroidism causes exertional rhabdomyolysis (tying-up) in horses.

Hyperthyroidism in horses. Historically, it was believed that hyperthyroidism did not occur in horses, but it has been reported recently in 2 horses. In the first case, a 21-year-old Arab gelding had a thyroid adenocarcinoma. In the second case, a 23-year-old gelding presented with cachexia and hyperactivity of one year's duration. The horse paced and circled almost constantly and had a ravenous appetite. A subcutaneous mass in the neck was subsequently shown after total excision to be a thyroid adenoma. Thyroid hormone supplementation was not required since plasma thyroid hormone concentrations returned to normal at 35 days post-operatively. Based on these 2 cases, it cannot be assumed that a horse with a thyroid enlargement will be normo- or hypothyroid, since hyperthyroidism does apparently occur rarely.

Treatment

There are numerous commercial thyroid supplements currently available. Because of the difficulty in accurately diagnosing hypothyroidism in the horse, the practitioner often must decide whether the clinical signs are compatible with hypothyroidism and then must treat the patient empirically with one of the available commercial supplements. Recommended dosage rates have not been validated by appropriately-designed studies. Foreman recommended an empirical dose of 30 grains (1950 mg or 1.95 g) of thyroid hormone replacement tablets twice daily in the feed of horses with myopathy problems based on experience and clinical impression that the horses' performance improved.³⁷ Chen and co-workers extrapolated the common canine dose of 20 $\mu\text{g}/\text{kg}$ to the horse to derive a dose of 10 mg T4/horse/day. During treatment, it is advisable to recheck total and free serum T3 and T4 concentrations at regular intervals while assessing the clinical response. The dose should then be titrated as necessary. No recommendations for sampling times of serum T4 and T3 concentrations after administration of thyroid supplement were found in the literature. Based on knowledge gained in treating dogs, twice daily administration of thyroid hormone is probably preferable and endogenous TSH concentration is very beneficial in assessing response to therapy.

References and Footnotes. Available upon request.

