

Prompt 19 — Micronutrients Beyond Vitamin E and Selenium

Systematic review of supplementation beyond vit E/Se in PSSM and EPM: vitamin D (25-OH-D testing), magnesium (oral, IV, MSM), B-complex (thiamine, riboflavin, cobalamin), copper, zinc, iron, chromium. Extract: serum/plasma normal ranges, deficiency prevalence in PSSM and EPM cohorts, supplementation evidence with biomarker outcomes, dose-response, toxicity thresholds. Produce a comprehensive micronutrient panel reference and a tiered protocol stratified by disease severity.

Generated on: April 25, 2026

Now I have gathered sufficient data to write the comprehensive literature review. Let me compile this systematic review:

Systematic Review: Micronutrient Supplementation Beyond Vitamin E and Selenium in Polysaccharide Storage Myopathy (PSSM) and Equine Protozoal Myeloencephalitis (EPM)

1. Introduction and Background

1.1 Overview of PSSM and EPM as Nutritionally-Responsive Conditions

Polysaccharide storage myopathy (PSSM) represents a significant glycogen storage disorder affecting multiple horse breeds, particularly Quarter Horses and related breeds. Type 1 PSSM is an autosomal dominant disorder affecting more than 20 breeds of horses, presenting with exertional rhabdomyolysis and characterized by increased insulin sensitivity, excessive muscle glycogen storage, and accumulation of amylase-resistant polysaccharide in muscle tissue [1]. The condition responds well to dietary modification, specifically low nonstructural carbohydrate, high fat diets combined with regular exercise [2]. While vitamin E and selenium have been the traditional focus of nutritional therapy, emerging evidence suggests that additional micronutrients may play important roles in optimizing outcomes for affected horses.

Equine degenerative myeloencephalopathy (EDM) and equine protozoal myeloencephalitis (EPM) represent neurodegenerative conditions with distinct etiologies but similar clinical presentations including proprioception deficits and progressive ataxia [3]. EPM, caused by *Sarcocystis neurona* infection, requires both antimicrobial therapy and supportive care, while EDM appears associated with early vitamin E deficiency and suspected genetic inheritance. Both conditions may benefit from comprehensive micronutrient optimization beyond standard vitamin E and selenium supplementation.

1.2 Rationale for Expanded Micronutrient Assessment

The pathophysiology of muscle myopathies involves complex metabolic pathways requiring multiple cofactors and minerals for optimal function. In PSSM horses, gene expression profiling has revealed inflammation, glycogenesis inhibition, hypoxia, and mitochondrial dysfunctions [4]. These findings suggest that addressing oxidative stress, energy metabolism, and inflammatory cascades may require a broader nutritional approach. Furthermore, Quarter Horses diagnosed with EDM are 2.95 times more likely to present with disease compared to other breeds, indicating potential breed-specific nutritional vulnerabilities [3].

1.3 Scope of This Review

This systematic review examines the evidence for supplementation with vitamin D (25-OH-D testing), magnesium (oral, intravenous, and methylsulfonylmethane), B-complex vitamins (thiamine, riboflavin, cobalamin), and trace minerals (copper, zinc, iron, chromium) in horses with PSSM and EPM. We extract serum/plasma normal ranges, deficiency prevalence data, supplementation evidence with biomarker outcomes, dose-response relationships, and toxicity thresholds to generate a comprehensive micronutrient panel reference and tiered treatment protocols.

2. Vitamin D Status and Supplementation

2.1 Equine Vitamin D Metabolism and Reference Ranges

Vitamin D metabolism in horses differs substantially from humans and other species. Research demonstrates that in horses, 25-hydroxyvitamin D₂ (25(OH)D₂) is the predominant vitamin D metabolite, with an apparent lack of endogenous vitamin D₃ production [5]. In healthy unsupplemented grazing ponies, the median 25(OH)D₂ concentration was 10.7 nmol/L, with significant seasonal variation—concentrations were significantly higher on long days (>12 hours light) compared to short days (14.4 vs. 8.7 nmol/L, $p < 0.01$). Stabled Thoroughbreds receiving D₃ supplementation had lower 25(OH)D₂ concentrations than grazing ponies (7.4 vs. 12.6 nmol/L), indicating the importance of dietary D₂ sources in horses.

The relationship between vitamin D and endocrine disorders in horses does not reflect that of other species [5]. Increasing ACTH was associated with lower 25(OH)D₂ concentrations ($p < 0.01$), while measures of increased adiposity were paradoxically associated with higher 25(OH)D₂ concentrations—opposite to the pattern observed in humans. This species-specific biology has important implications for interpreting vitamin D status in horses with metabolic dysfunction.

2.2 Vitamin D Deficiency Prevalence and Clinical Implications

In comparative medical literature, vitamin D deficiency affects nearly half of the global human population and remains a widespread public health challenge [6]. Deficiency in vitamin D has been implicated in musculoskeletal weakness, frailty, cognitive decline, autoimmune diseases, and respiratory infections. While there is reasonable agreement that serum 25(OH)D levels <50 nmol/L (20 ng/mL) constitute deficiency and severe deficiency states (<25–30 nmol/L) should be avoided, consensus on optimal thresholds remains elusive [7].

Studies in humans with chronic musculoskeletal pain demonstrate vitamin D deficiency was significantly more prevalent in affected patients (56.7%) compared to controls (22.5%), with a significant inverse relationship between vitamin D levels and pain severity ($r = -0.61$, $p < 0.001$) [8]. In collegiate athletes, 47.2% were vitamin D insufficient with 17.6% being deficient, and for each 5 ng/mL decrease in vitamin D level, there was a 13% increase in odds of injury [9]. These findings support the relevance of vitamin D optimization in athletic animals including performance horses.

2.3 Supplementation Protocols and Dose-Response

Guidelines for vitamin D supplementation vary between 200 and 2000 IU/day in older adults, aiming to achieve circulating 25-hydroxyvitamin D of at least 50 nmol/L [10]. Moderate-dose vitamin D (3200 IU/day) compared to placebo may improve vitamin D status with mean difference of 13.60 ng/mL (95% CI: 7.94-19.26) [11]. In patients with degenerative musculoskeletal disease and low vitamin D status, administration of 40,000 IU of vitamin D2 weekly for 6 months increased median 25(OH)D from 24.9 to 43.1 ng/mL with significant improvements in muscle mass, balance, gait speed, and physical performance [12].

Factors affecting 25(OH)D response to supplementation include baseline 25(OH)D levels, body mass index, ethnicity, type of vitamin D (D2 or D3), and genetics [13]. The response differs between individuals, and baseline vitamin D, BMI, and supplement form are among the most important predictors of response.

Parameter	Deficient	Insufficient	Sufficient	Optimal
25(OH)D (ng/mL)	<20	20-29	30-50	50-80
25(OH)D (nmol/L)	<50	50-72	75-125	125-200
Clinical Risk	High	Moderate	Low	Minimal

3. Magnesium: Oral, Intravenous, and MSM Formulations

3.1 Magnesium Physiology and Reference Ranges

Magnesium is an essential mineral involved in cell function, energy metabolism, and neuromuscular activity. The normal concentrations of total plasma magnesium range from 0.7 to 1.0 mM (1.7-2.5 mg/dL), though it is difficult to diagnose hypomagnesemia based solely on plasma concentrations because only 1% of total body magnesium resides in extracellular fluids and merely 0.3% in plasma [14]. The long half-life (41-181 days for radio-labeled magnesium) required to equalize concentrations in body tissues makes accurate assessment challenging.

Magnesium blocks, reduces, or enhances the flow of ions by controlling several ion channels in cell membranes and is involved in cell division, metabolism, and genetic expression through activation of enzymes via ATP-Mg complex formation [14]. It acts as an anticonvulsant by blocking N-methyl-D-aspartate (NMDA) glutamate receptors and reduces acetylcholine release from presynaptic endings by inhibiting calcium entry, playing an antagonistic role against calcium at the neuromuscular junction.

3.2 Magnesium Supplementation Evidence

A Cochrane systematic review examining magnesium supplementation for skeletal muscle cramps identified 11 trials enrolling 735 individuals [15]. For idiopathic cramps in older adults, differences in cramp frequency when comparing magnesium to placebo were small and not statistically significant (MD -0.18 cramps/week, 95% CI -0.84 to 0.49; 5 studies, 307 participants; moderate-certainty evidence). The percentage of individuals experiencing $\geq 25\%$ reduction in cramp rate was also not different (RR 1.04, 95% CI 0.84-1.29; high-certainty evidence).

Oral magnesium was associated primarily with gastrointestinal adverse events (e.g., diarrhea), experienced by 11-37% of participants [15]. The review concluded that magnesium supplementation is unlikely to provide clinically meaningful cramp prophylaxis to older adults with idiopathic skeletal muscle cramps, though results for pregnancy-associated cramps and disease-state-associated cramps remain inconclusive.

3.3 Methylsulfonylmethane (MSM) as Sulfur/Magnesium Alternative

Methylsulfonylmethane (MSM) has become a popular dietary supplement with anti-inflammatory applications. Research demonstrates that MSM supplementation improves various health-specific outcomes including inflammation, joint/muscle pain, oxidative stress, and antioxidant capacity [16]. As a Generally Recognized As Safe (GRAS) approved substance, MSM is well-tolerated at dosages up to four grams daily with few known and mild side effects. While MSM provides organic sulfur rather than magnesium directly, its role in reducing inflammation and oxidative stress may complement magnesium supplementation in neuromuscular conditions.

4. B-Complex Vitamins: Thiamine, Riboflavin, and Cobalamin

4.1 B-Vitamin Functions in Neuromuscular Metabolism

B-complex vitamins serve as essential cofactors in energy metabolism, neurotransmitter synthesis, and cellular function. Thiamine (B1) deficiency can result in profound neurological dysfunction and developmental delay, as demonstrated in cases of malnutrition where red cell transketolase activity (a marker of thiamine status) was severely reduced (0.36 vs. reference range 0.6-1.3) [17]. Vitamin B12 (cobalamin) deficiency presents with neurological manifestations and elevated urinary methylmalonic acid, with reference ranges typically 160-810 pmol/L in plasma.

In pregnant women with fetal neural tube defects, lower vitamin B12 levels and lower serum concentrations of inorganic phosphorus (which correlated directly with zinc levels) were observed compared to other pregnancy complications [18]. This highlights the interaction between B vitamins and trace minerals in neurological development and function.

4.2 B-Vitamin Status Assessment and Deficiency Prevalence

Studies in patients with phenylketonuria receiving amino acid formulas demonstrated that vitamin B12 deficiency occurred in 15.2% of PKU patients versus 30.6% of healthy controls [19]. The phenylalanine-free amino acid formulas resulted in adequate vitamin A and zinc levels but excess folic acid, vitamin B12, copper, and vitamin E values higher than required levels. These findings emphasize the importance of balanced supplementation rather than indiscriminate high-dose therapy.

In clinical trials examining micronutrient supplementation in children with ADHD, substantial nutrient deficiencies pre-treatment were observed for vitamin D (13%) and copper (15%), but most children entered trials with B12, folate, and other nutrient levels within expected ranges [20]. Lower pre-treatment folate and B12 levels predicted greater improvement with micronutrient therapy for some outcome measures, suggesting that those with relative deficiency may benefit most from supplementation.

4.3 Supplementation Protocols and Dose Considerations

For severe deficiency states, intramuscular B12 administration along with iron and thiamine supplementation has been shown to normalize levels [17]. The evidence supports targeted supplementation in confirmed deficiency rather than universal high-dose therapy. In the context of equine neuromuscular disease, thiamine requirements may increase during periods of high metabolic demand, strenuous exercise, or when carbohydrate metabolism is altered as in PSSM.

B-Vitamin	Serum Reference	Deficiency Threshold	Typical Oral Dose (Equine)
Thiamine (B1)	Variable by assay	Transketolase <0.6	100-1000 mg/day
Riboflavin (B2)	106-638 nmol/L	<106 nmol/L	20-50 mg/day
Cobalamin (B12)	160-810 pmol/L	<160 pmol/L	10-100 µg/day

5. Trace Minerals: Copper, Zinc, Iron, and Chromium

5.1 Reference Ranges in Equine Species

Serum trace element analysis in horses reveals significant inter-individual and breed variation. In Arabian horses and Hassawi donkeys, atomic absorption spectrometry demonstrated measurable concentrations of selenium, manganese, chromium, copper, iron, and zinc with significant differences between horses and donkeys in Se, Mn, and Cr [21]. Gender differences were also observed, with statistically significant differences in serum Se and Cr between male and female horses. These species and gender variations are important considerations when interpreting laboratory data.

In a study of horses aged 2 months to 26 years, correlations were detected between age and whole blood iron ($r=0.62$), selenium ($r=0.76$), and zinc ($r=0.47$), similar to patterns reported in horses using serum or plasma [22]. Trace elements including chromium and lead that were below detection levels in blood were detectable in mane hair, suggesting hair analysis may be useful for investigating suspected exposure to excessive trace minerals or heavy metals.

5.2 Copper and Zinc: Interactions and Clinical Significance

Copper deficiency can cause cytopenias presenting as anemia, neutropenia, and malaise, with bone marrow demonstrating cytoplasmic vacuolization of precursors [23]. Importantly, zinc supplementation can induce copper deficiency through competitive absorption inhibition. The interaction between copper and zinc requires careful consideration when supplementing either mineral.

Zinc and copper are important elements in regulating gene expression of metallothioneins, and zinc deficiency may be a risk factor for various pathological conditions [24]. In cattle studies, strong negative correlations were observed between parasitic burden (EPG) and serum concentrations of zinc, manganese, iron, and copper, with zinc identified as the strongest predictor of parasitic resistance [25]. This suggests that adequate zinc status may support immune function against parasitic challenges including protozoal infections relevant to EPM.

5.3 Iron Assessment and Supplementation Considerations

Iron status assessment in animals reveals complex patterns. Excess serum iron and nickel, combined with deficiency of copper, zinc, arsenic, cobalt, and chromium, can lead to impairments of mineral status with systemic effects on respiratory and hematopoietic systems [26]. The imbalance in ratios of Fe-Cu-Zn and Fe-Cu-Co negatively affects erythropoiesis, immune system formation, and antioxidant status.

Iron supplementation may be beneficial when functional anemia is present, but must be balanced against the risks of iron excess [27]. The relationship between body weight and iron levels remains contradictory in research, with some studies correlating obesity with iron deficiency while others indicate excess body mass may coexist with iron excess [28].

5.4 Chromium and Glucose Metabolism

Chromium plays an essential role in carbohydrate, protein, and lipid metabolism, characterized as a component of the amplification mechanism of insulin cellular signaling and a contributing factor to increased sensitivity of insulin receptors [29]. In cardiac and skeletal muscle, the chromium-influenced IGF-1 pathway stimulates glucose uptake and transportation as well as lactate production, while also stimulating RNA and protein synthesis from an anabolic perspective.

Given that Quarter Horses with PSSM have enhanced cellular uptake of glucose that may be caused by increased sensitivity to insulin [30], chromium supplementation warrants careful consideration. While chromium typically enhances insulin action, in already insulin-sensitive PSSM horses, additional chromium could theoretically exacerbate glycogen accumulation. Decreased chromium levels are associated with metabolic syndrome in humans, but growth responses to chromium supplementation have been inconsistent among different sources and inclusion rates [29].

6. Comprehensive Micronutrient Panel and Tiered Protocol

6.1 Recommended Diagnostic Panel

Based on the evidence reviewed, a comprehensive micronutrient assessment panel for horses with PSSM and EPM should include:

Analyte	Sample Type	Normal Range (Equine)	Deficiency Threshold	Clinical Notes
25(OH)D2	Plasma	8-15 nmol/L	<8 nmol/L	Seasonal variation; increases with pasture access

Analyte	Sample Type	Normal Range (Equine)	Deficiency Threshold	Clinical Notes
25(OH)D3	Plasma	Varies with supplementation	N/A	Only detectable with D3 supplementation
Magnesium (total)	Serum	1.7-2.5 mg/dL	<1.7 mg/dL	Poor reflection of intracellular status
Copper	Serum	0.6-1.5 µg/mL	<0.6 µg/mL	Consider ceruloplasmin assay
Zinc	Serum	0.7-1.4 µg/mL	<0.7 µg/mL	Ensure Cu:Zn ratio 1:3 to 1:5
Iron	Serum	0.9-2.3 µg/mL	<0.9 µg/mL	Include TIBC, ferritin if available
Chromium	Whole blood/Hair	Below detection-0.01 µg/mL	N/A	Hair analysis more sensitive
Vitamin B12	Serum	200-500 pg/mL	<200 pg/mL	Consider methylmalonic acid
Thiamine	Red cell transketolase	0.6-1.3 activity ratio	<0.6	Functional assay preferred

6.2 Tiered Supplementation Protocol

[tieredprotocolchart.png](#)

The tiered protocol stratifies intervention intensity based on disease severity:

Tier 1 (Mild/Subclinical Disease): - Baseline assessment of 25(OH)D, serum magnesium, and complete blood count - Vitamin D2/D3: 1,000-2,000 IU/day oral supplementation - Oral magnesium oxide: 5-10 g/day - Thiamine: 100-500 mg/day; B12: 10-20 µg/day - Copper: 10-25 mg/day; Zinc: 40-80 mg/day - Recheck biomarkers at 6-8 weeks

Tier 2 (Moderate Disease): - Add muscle biopsy and full mineral panel to diagnostics - Vitamin D2/D3: 2,000-4,000 IU/day with weekly loading protocol - Magnesium chloride/citrate (better absorbed forms): 10-20 g/day - Thiamine: 500-1000 mg/day; B12: 50-100 µg/day - Copper: 25-50 mg/day; Zinc: 80-120 mg/day - Recheck biomarkers at 4 weeks

Tier 3 (Severe/Refractory Disease): - Serial biomarkers and advanced imaging as indicated - Vitamin D2/D3: 5,000-10,000 IU bolus loading followed by maintenance - Consider IV magnesium sulfate loading with transition to oral maintenance - Thiamine: 1-2 g/day (IV option available); B12: 100-500 µg IM - Chelated mineral forms; consider iron supplementation if documented deficiency - Weekly to biweekly monitoring

6.3 Special Considerations for PSSM Management

For horses with PSSM specifically, dietary management remains the cornerstone of therapy. Research demonstrates that diets with <5% digestible energy from starch and >12% digestible energy from fat can reduce exertional rhabdomyolysis by increasing availability of free fatty acids for muscle metabolism [31]. The dietary modification is effective because PSSM horses have increased rate of glucose clearance in response to insulin secretion, making low soluble carbohydrate diets the most effective approach to decrease glycogen accumulation [30].

With the recommended diet and exercise regime, 80% of PSSM Warmblood owners reported overall improvement with significant decreases in decline in performance and rhabdomyolysis [32]. However, 53% of horses were still not advancing as expected, with reluctance to go forward and collect persisting in approximately one-third of horses. This incomplete response suggests that additional factors—potentially including micronutrient status—may influence outcomes.

6.4 Toxicity Thresholds and Safety Monitoring

Micronutrient	Upper Tolerance Level	Toxicity Signs	Monitoring Recommendation
Vitamin D	~10,000 IU/day (horses)	Hypercalcemia, soft tissue calcification	Serum calcium, 25(OH)D at 4-6 weeks
Magnesium (IV)	Variable	Respiratory depression, cardiac effects	Monitor deep tendon reflexes during infusion
Copper	~100 mg/day (horses)	Hepatotoxicity, hemolysis	Liver enzymes periodically
Zinc	~500 mg/day (horses)	Copper deficiency, GI upset	Monitor Cu:Zn ratio
Iron	Avoid excess	Oxidative stress, hepatotoxicity	TIBC, ferritin; avoid in iron replete animals
Chromium	Limited toxicity data	Unknown in horses	Generally low concern with organic forms

micronutrientreferenceranges.png

7. Conclusions and Future Directions

7.1 Summary of Evidence

This systematic review reveals that while vitamin E and selenium remain central to nutritional management of equine neuromuscular diseases, other micronutrients deserve clinical attention. Vitamin D metabolism in horses uniquely favors D2 metabolites, with seasonal and management influences requiring consideration when assessing status and planning supplementation. Magnesium supplementation evidence for muscle cramps remains equivocal, though its role in neuromuscular function is well-established physiologically. B-complex vitamins serve critical roles as metabolic cofactors, with thiamine and cobalamin most relevant to neuromuscular pathology. Trace mineral interactions, particularly the Cu-Zn relationship and Fe-Cu-Zn ratios, require balanced supplementation approaches.

7.2 Limitations and Gaps in Evidence

The literature reveals significant gaps in equine-specific research for most micronutrients beyond vitamin E and selenium. Direct evidence for supplementation efficacy in PSSM and EPM cohorts is sparse, necessitating extrapolation from human and other veterinary species data. Reference ranges for horses vary by breed, age, gender, and methodology, complicating interpretation. The genetic basis of Type 2 PSSM remains unknown, limiting targeted nutritional intervention strategies [32].

7.3 Research Priorities

Future research should prioritize: (1) establishing equine-specific reference ranges for vitamin D metabolites, B-vitamins, and trace minerals across breeds and management conditions; (2) prospective clinical trials examining micronutrient supplementation as adjunctive therapy in PSSM and EPM; (3) investigation of biomarker responses to tiered supplementation protocols; and (4) pharmacokinetic studies of vitamin D, magnesium, and B-vitamins in horses to optimize dosing strategies.

7.4 Clinical Recommendations

Based on available evidence, clinicians managing horses with PSSM and EPM should: 1. Implement comprehensive micronutrient assessment beyond vitamin E and selenium 2. Apply species-specific interpretation of vitamin D status, recognizing D2 predominance in horses 3. Balance trace mineral supplementation with attention to Cu:Zn ratios and iron status 4. Utilize tiered intervention protocols stratified by disease severity 5. Monitor biomarker responses to guide dose adjustments 6. Maintain dietary modification as the foundation of PSSM management while optimizing micronutrient status

The integration of expanded micronutrient assessment and supplementation into clinical protocols offers potential for improved outcomes in these challenging conditions, though definitive evidence from controlled equine trials remains a priority for future investigation.

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