



## Copper Nutrition in Camelids – Part 1

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Copper (Cu) is another one of the essential microminerals required by llamas and alpacas as well as all other animals and people to help maintain normal body functions. Similar to the discussion in a previous column regarding selenium, Cu nutrition is a double-edged sword being associated with both deficiency and toxicity disease concerns. Although all microminerals are of importance, Cu is receiving more attention as a result of the potential toxicity concerns with llamas and alpacas. There is evidence of increasing Cu content in forages and feeding with other copper-containing supplements (pellets and mineral) may predispose animals to a greater risk for toxicity problems. The objective of this column is to provide an overview of Cu nutrition by describing biologic functions and associated deficiency and toxicity disease conditions in llamas and alpacas. A subsequent column will address Cu requirements, assessment of Cu status, and dietary supplementation practices, especially concerns relative to toxicity risks.

### **Biological Roles**

Essentiality of Cu in animals was not discovered until 1928, though it had been discovered in animal and plant tissues much earlier. Copper performs a number of essential roles in the body as a component of various proteins (e.g., metallo-enzymes) that require Cu to sustain their biologic functions. Some examples of Cu metallo-enzymes include ceruloplasmin, tyrosinase, lysyl oxidase, cytochrome C oxidase, and superoxide dismutase. Through the action of

these metallo-enzymes, Cu has been associated with iron regulation and red blood cell function, cellular respiration, bone and connective tissue formation, hair pigmentation, nerve tissue and cardiac development, and immune function.

Ceruloplasmin is a blood protein with multiple functions and contains seven copper atoms, thus accounting for a majority of copper in blood. Ceruloplasmin converts stored iron into a form that can be incorporated into hemoglobin, the pigment responsible for oxygen transport in red blood cells. Ceruloplasmin also plays an important role in the non-specific immune response and its blood concentration will be elevated in response to an infectious agent. Functional activity of most cell types responsible for the various immune system responses are influenced by Cu through superoxide dismutase activity.

Of interest to llama and alpaca owners, Cu plays an important role in fleece coloration and quality. Tyrosinase (polyphenyl oxidase) is the enzyme responsible for the formation of melanin, a pigment responsible for hair and skin coloration. Hair or fleece would appear lighter in color or “bleached out” without the presence of melanin. Cross linkages of disulfide groups within the keratin structure of hair provide the physical properties of fleece and are dependent upon Cu. Wool from sheep with copper deficiency are described as having “steely wool” where the crimp has been lost and the fiber is straight.

Normal development of bone and connective tissue is dependent upon the

copper-dependent enzyme lysyl oxidase. This enzyme is responsible for modifying specific amino acids within the collagen protein structure that facilitates cross linkages between collagen fibers within connective tissue. These cross linkages impart properties of rigidity or elasticity to the collagen structure. Rigid connective tissue provides the scaffolding for mineralization in the development of bone. Elastic properties of collagen are seen in the large blood vessels such as the aorta, which must withstand wide fluctuations in pressure in circulating blood.

The cell's ability to generate energy through the transfer of electrons to the final receptor oxygen to form water is one of the functions of cytochrome C oxidase. Integrity of the nervous system is dependent upon the specialized phospholipid coating (myelin) around nerve fibers facilitating transmission of nerve signals. Myelin formation in the brain and spinal cord is related to cytochrome C oxidase activity. Besides the structural effects on nervous tissue, Cu is linked to nervous and cardiac tissue communications through its effect on production of neurotransmitters and heart muscle fiber (myofibril) development. Both cytochrome C oxidase and dopamine- $\beta$ -monooxygenase are responsible for these biologic functions of Cu.

### **Deficiency Diseases**

With the number of biological functions attributed to Cu, a wide range of diseases has been associated with a deficient nutrient status. A most common Cu deficiency disease that occurs in a wide range of animals is anemia or a lack of red blood cells. Anemia can be characterized by the size and pigment (hemoglobin) content of red blood cells. In other ruminants, Cu deficiency can induce a macrocytic (large cell size), hypochromic (low hemoglobin) anemia due to low ceruloplasmin activity.

Anemia and poor condition attributed to Cu deficiency has been reported in two llamas (14 and 23 months of age) (Andrews and Cox, 1997). Although anemia can result from a number of nutritional and non-nutritional insults, affected llamas in this report had low blood Cu concentrations (3.8 - 8.3  $\mu\text{g/dL}$ ) and responded to Cu supplementation with resulting increased blood Cu concentrations (66.7 – 82.6  $\mu\text{g/dL}$ ). These Cu concentrations are consistent with recognized Cu deficiency in other species and are below reported values (mean 35.6, range 16.5 – 55.3  $\mu\text{g/dL}$ ) for healthy llamas (Smith et al., 1998).

Copper deficiency has been associated with neurologic degeneration in sheep as a result of abnormal myelin formation with resulting disease signs of muscular weakness of the legs and inability to walk normally (ataxia). There have been three different published reports of possible association between Cu deficiency and neurologic disease and ataxia in llamas and alpacas (Smith, 1989; Palmer et al., 1980; Morgan, 1992). Presenting signs in the affected animals included hind limb ataxia, paralysis or head tremors. Blood Cu concentrations of the affected animals in these reports were not in the deficient range; however, blood Cu is not always a reliable measure of Cu status. Response to Cu supplementation in these cases was not well defined, thus questioning whether or not this truly was a Cu deficiency disease process. In one of the reports, a 6-mo old llama was described with progressive paralysis and liver and kidney Cu concentrations were found to be deficient. More evidence is needed to determine if there is a role for Cu deficiency in neurologic disease of camelids, similar to that described for sheep.

Other potential Cu-deficiency diseases have not been reported in llamas and alpacas, though there is no indication that there is potential for such diseases. One

might surmise there is the possibility for achromotrichia (loss of fleece pigmentation) and fleece structural changes in llamas and alpacas similar to what is seen in sheep and other species with Cu deficiency. Bone development abnormalities (similar to rickets), blood vessel ruptures, and heart degeneration are other recognized Cu deficiency diseases, but these are not seen in all species. Copper deficient diseases will vary among animal species.

Up to this point, the disease conditions discussed are classified as clinical disease syndromes. Clinical disease is characterized as the “classical” disease processes associated with a specific nutrient. In contrast to clinical disease is what is termed subclinical disease. Subclinical disease is described as non-specific consequences of a nutrient being marginally deficient or toxic. Subclinical Cu deficiency is associated with impaired immune response and greater susceptibility to disease, reduced reproductive fertility, and poor growth or lactation. Clinical disease is more readily identified, but is not near as prevalent as subclinical disease. With difficulties in assessing Cu status using blood concentrations (to be discussed in part 2), subclinical disease becomes a difficult process to diagnose.

### **Toxicity Disease**

As I discussed in a previous column in addressing selenium, toxicity resulting from excessive intake of a trace mineral can also produce disease problems. Sheep are well known to be extremely sensitive to excess dietary Cu (>10 mg/kg); however, camelids do not seem to be as keenly sensitive but are prone to toxicity. At least four published case studies have reported Cu toxicity or suspected toxicity in llamas and alpacas (Junge and Thornburg, 1989; Mullaney et al., 1996; Weaver et al., 1999; Carmalt et al., 2001). I have been associated with a number of clinical situations in which Cu toxicity

was highly suspected and I am aware of other cases seen by other veterinarians. It would seem that Cu toxicity is a disease of greater concern for llamas and alpacas. The challenge is being able to recognize disease risk early and initiate appropriate dietary changes as there is no treatment once the disease process has started.

Copper toxicity is the result of the highly reactive nature of the Cu ion when not protectively bound in tissues or blood. Copper like most minerals is a strong oxidizing agent that can damage cellular membranes and proteins. In most situations Cu toxicity is a progressive disease process where excess dietary Cu accumulates in the liver until it becomes saturated. The liver is the primary mineral storage organ of the body and contains special protein molecules capable of binding minerals and keeping them isolated from doing any damage to the surrounding tissues. Stored Cu is inefficiently excreted through bile produced in the liver and transported to the intestinal tract to be lost in fecal matter. The ability to excrete Cu is species dependent and accounts for the observed differences in sensitivity to Cu toxicity. Once the liver has become saturated with stored Cu, excess will spill out into the liver and blood wrecking oxidative havoc.

Clinical Cu toxicity in sheep is characterized by massive breakage of red blood cells (hemolysis) due to oxidative damage from the Cu ion released into the bloodstream. With hemolysis there is leakage of free hemoglobin into the blood (hemoglobinemia) and urine (hemoglobinuria). Hemoglobin in urine will induce damage to the kidneys. The hemolytic crisis stage of the disease is nearly always fatal. The disease process is different in llamas and alpacas as the “hemolytic crisis” has not been reported or seen in field cases. The common theme in llama and alpaca Cu toxicity cases is the

documentation of severe and widespread degenerative changes (necrosis) in the liver. This is a different process than hepatic lipidosis (fatty liver). Liver necrosis may or may not be associated with elevated blood enzyme activities assessing liver function. Affected llamas and alpacas will have highly elevated blood (>200 µg/dL) and liver (>600 µg/g dry weight) Cu concentrations as well as elevated kidney Cu concentrations.

Typically blood and kidney Cu concentrations are not highly elevated until the final initiation of the disease process; therefore they may not be useful in diagnosing potential risk. Additionally kidney Cu concentrations are only determined in animals that have died. The difficulty in dealing with this disease is that animals may only show minimal signs of poor doing prior to the final demise. Stress factors or previous liver disease may precipitate the disease.

Key to understanding and preventing Cu toxicosis is nutritional management practices. Based on these published reports and the documentation of dietary factors, llamas and alpacas are seemingly prone to Cu toxicity when fed diets with greater than 20 mg/kg (ppm) total Cu and a high ratio (16:1) of Cu to molybdenum (Mo). Molybdenum is a trace mineral that plays an important role in dietary Cu availability. My next column will address issues of Cu availability, requirements, and feeding practices to prevent these disease issues.

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