

## Copper deficiency in ruminants (Proceedings)

Copper deficiency occurs when the diet contains an abnormally low amount of copper (primary copper deficiency) or when copper absorption or metabolism is adversely affected (secondary copper deficiency).

- If inadequate amounts of copper are available to tissues in the form of essential metalloenzymes, the signs of copper deficiency (hypocuprosis) may occur.

Clinical signs in ruminants include diarrhea, decreased weight gain, unthrifty appearance, anemia, changes in coat color (achromotrichia) or wool quality, anemia, spontaneous fractures, lameness (epiphysitis) and demyelination (enzootic ataxia of sheep and goats, or swayback). One of these syndromes usually predominates in a given herd.

Secondary copper deficiency is associated with high dietary levels of molybdenum, sulfates, zinc, iron, or other compounds. Secondary copper deficiency often presents with clinical signs of diarrhea and weight loss or unthriftiness. It has been called teart, peat scours, renguerra, pine, and salt lick disease. Salt sickness in Florida appears to be the result of combined copper and cobalt deficiencies.

### Epidemiology

-Copper deficiency can occur when diets are inadequate in copper or contain excess amounts of interfering substances, particularly sulfates and molybdenum.

-Forages and water can be sources of molybdenum, sulfur, and sulfate.

**-To avoid primary copper deficiency, pasture (dry matter) should contain over 5 ppm of copper, with 3 to 5 ppm considered marginal, and less than 3 ppm deficient.**

**Soil copper concentrations are generally slightly lower than that of the harvested forage.**

-Molybdenum adversely affects plant uptake of copper. Forage molybdenum concentrations greater than the copper concentrations often lead to secondary copper deficiency, even when forage copper is adequate.

-Since copper content in grasses and legumes can be different, forage samples must be randomly selected to reflect dietary intake.

-Forage copper concentrations as high as 12 to 27 ppm have been associated with copper deficiency when molybdenum levels are high.

**-The critical ratio of copper to molybdenum in feeds is 2:1, with 5:1 recommended for sheep and 5:1 to 10:1 for grazing cattle.**

## Pathogenesis

dietary deficiency of copper results in hypocuprosis and eventual clinical signs. Also, a variety of conditions can decrease copper absorption from the gastrointestinal tract (large intestine in sheep and small intestine in cattle). The interactions between dietary copper, molybdenum, and sulfates (or sulfur) are important.

-Excess dietary molybdenum can lead to the formation of sparingly soluble **Cupric molybdates in the rumen** that are **not absorbed from the intestine**.

The addition of **excess sulfur or sulfates in the diet and/or water** can result in the formation of **insoluble copper thiomolybdates in the rumen**. The interactions between these three elements are complex.

The infertility seen with secondary copper deficiency may be due to excess circulating oxythiomolybdates which interfere with the release of luteinizing hormone.

It is important to note that at low sulfur concentrations in the diet

-Excess molybdenum has a minimum effect on decreasing copper absorption. Even when no dietary molybdenum or sulfates are present, only about 5% of ingested copper is normally absorbed.

-Excessive calcium in the diet, particularly in the form of limestone, decreases copper absorption.

- Excessive iron, 30 mg/kg of body weight or 1200 ppm in the diet of calves, reduces copper absorption.

Overgrazing, with the subsequent ingestion of excess soil also decreases copper absorption.

In addition, excess cadmium (3 to 7 ppm) or excess zinc (100 to 400 ppm) reduces hepatic copper concentration, probably through the combined effect of decreased absorption and competition with copper for hepatic metallothionein.

It had been suggested that excess dietary selenium might interfere with copper absorption and/or utilization, recently, this has been shown not to occur.

Copper is an essential component of a number of mammalian enzymes. Some of the medically important copper-containing enzymes are

(1) the cytosol form of superoxide dismutase (copper and zinc),

(2) cytochrome oxidase ,

(3) lysyl oxidase,

(4) ascorbic acid oxidase, and

(5) ceruloplasmin.

In addition, normal copper nutrition appears essential for iron absorption and transportation of iron to the liver and reticuloendothelial system and is thus necessary for normal hemoglobin formation. The precise pathophysiology of

most of the copper deficiency syndromes is not known. However, the central role of copper in preventing cellular oxidative damage and its role in iron and sulfur metabolism are probably important.

## Clinical syndromes and differential diagnosis

-Profuse watery diarrhea with poor weight gains and/or weight loss is a common syndrome seen in ruminants with copper deficiency. When it occurs on boggy pastures that contain high concentrations of molybdenum,

Decreased weight gains or weight loss as a herd problem can have many other causes, including parasitism, trace mineral deficiencies (selenium, cobalt), protein calorie malnutrition, and Johne's disease.

- A syndrome characterized by epiphyseal enlargement, stiffness, and unthriftiness is seen in young ruminants and is the result of copper deficiency and is sometimes called pine.

- Copper deficiency can cause spontaneous fractures in ruminants.

The incidence of sway back can vary greatly among breeds of sheep, reflecting the genetic differences in copper metabolism both between and within breeds of sheep. The disease occurs in several forms.

- A congenital form, **cerebrospinal swayback**, occurs only when the copper deficiency is extreme. Affected lambs are born dead or weak and unable to stand and suck. Incoordination and erratic movements are more evident than in enzootic ataxia and the paralysis is spastic in type.

Blindness also occurs occasionally. There is softening and cavitation of the cerebral white matter and this probably commences about day 120 of gestation.

-**Progressive (delayed) spinal swayback** begins to develop some weeks after birth with lesions and clinical signs appearing at 3-6 weeks of age.

-**Postnatal acute fatal swayback** may be a third form of the disease It resembles the more usual delayed form, but develops suddenly.

There is a sudden onset of recumbency with death occurring 1-2 days later due to acute swelling of the cerebrum.

- Enzootic ataxia affects only unweaned lambs. In severe outbreaks, the lambs may be affected at birth, but most cases occur in the 1-2-month age group. The severity of the paresis decreases with increasing age at onset. Lambs affected at birth or within the first month usually die within 3-4 days.

-The disease in older lambs may last for 3-4 weeks and survival is more likely, although surviving lambs always show some ataxia and atrophy of the hindquarters.

-The first sign to appear in enzootic ataxia is incoordination of the hindlimbs, appearing when the

- lamb is driven. Respiratory and cardiac rates are also greatly accelerated by exertion .
- As the disease progresses, the incoordination becomes more severe and may be apparent after walking only a few yards.
  - There is excessive flexion of joints, knuckling over of the fetlocks, wobbling of the hindquarters and finally falling.
  - The hindlegs are affected first and the lamb may be able to drag itself about in a sitting posture. When the forelegs eventually become involved recumbency persists and the lamb dies of inanition.
  - There is no true paralysis, the lamb being able to kick vigorously even in the recumbent stage. The appetite remains unaffected.
- Inadequate keratinization of wool and achromotrichia is the result of imperfect oxidation of free thiol groups during hair growth and keratinization. Subsequently, the wool fibers do not crimp normally, and they appear to be "stringy" or "kinky".
  - A copper containing enzyme, tyrosinase (polyphenyloxidase), is needed to convert tyrosine to melanin. With copper deficiency, this conversion is slow and hair is lighter in color than normal (achromotrichia). Loss of wool crimp and pigmentation changes in sheep or cattle, respectively, occur late in the course of copper deficiency.
- In addition to the above clinical syndromes that may occur alone or jointly, deficiency may be associated with anemia (altered iron metabolism) or infertility. Infertility is probably multifactorial and may not respond to an increase in copper intake alone.
- Copper deficiency also seems to result in decreased immune function in ruminants

### **Clinical pathology and diagnosis**

The primary site of copper reserves is the liver. Normal liver copper concentrations in cattle are approximately 60 to 120 ug/g (ppm) and in sheep 80 to 200 ug/g on a dry weight basis (dry matter basis; DMB).

Hepatic copper concentrations as high as 250 ug/g DMB are not unusual in supplemented ruminants (even over 350 ug/g DMB in sheep).

- Blood copper concentrations can be maintained near normal until hepatic copper concentration falls to less than 35 ppm DMB, at which time the serum copper concentration invariably begins to decrease.

- When using blood samples for copper determination, serum or plasma is normally preferred.

- Plasma copper concentration is usually about 5% greater than an identical serum copper concentration.

- Normal serum copper is 0.7 to 1.2 ppm (ug/ml).

-Serum or plasma copper concentrations of 0.4 ppm or less are considered as evidence of deficiency.

- Values of 0.4 to 0.7 ppm are marginal and are difficult to interpret.

Approximately 50% to 90% of the copper in serum or plasma is present in ceruloplasmin.

-The remainder is bound to albumin or amino acids.

The correlation between serum copper and serum ceruloplasmin was found to be weak (0.50); thus ceruloplasmin is not commonly used to aid in diagnosing copper deficiency.

Hepatic copper concentration is the preferred diagnostic sample and is easily secured at necropsy.

Hepatic copper values less than 35 ppm DMB are considered deficient.

surgical biopsy is necessary for live patients, and, since laboratories generally require 1 g or more of tissue, a biopsy

- In sheep, serum and liver copper concentrations are the same for lambs (1 week of age) and adults. The plasma copper levels in lambs are low at birth, but rise to adult values by 1 to 7 days of age.

- Milk is a poor source of copper, containing only 0.2 to 0.6 ppm in normal ewes and 0.01 to 0.02 ppm in severely copper deficient ewes or cows.

Milk copper in cattle is 0.05 to 0.2 ppm. To make matters worse, molybdenum is concentrated in milk.

-Response trials using injectable copper are also a valid means of diagnosis.

## **ILL-THRIFT IN HILL LAMBS**

**A** condition of ill-thrift due to copper deficiency has been described in young lambs suckling ewes on improved bill pasture.

- The condition in the lambs is characterised by poor weight gains and poor fleeces which are stringy, sparse and grey in colour.

-Hypocupraemic lambs have also been found to be more susceptible to bone fractures than normal controls.

although histological examination revealed that the bones of both groups were osteoporotic.

- It was considered that the copper deficiency was induced by the high levels of molybdenum and sulphur in the reseeded pasture.

-The ewes, although also hypocupraemic, were clinically normal, with normal fertility, conception rates and body condition.

## **Enzootic Ataxia and Swayback**

Nutritional copper deficiency can lead to neuronal degeneration and secondary demyelination in the CNS and result in progressive paresis of young lambs and kids.

- The term swayback is applied to the congenital form of this condition,
- while enzootic ataxia refers to the condition if it develops after birth

### **Etiology**

In sheep, nutritional copper deficiency of the ewe during the second half of pregnancy leads to **abnormal maturation and subsequent degeneration of neurons and myelin in the developing fetus and the lamb postnatal.**

It is very likely that caprine enzootic ataxia and swayback are metabolic diseases of complex origin with conditioned copper deficiency .

- **Epidemiology**
- Copper deficiency in goats -can either be primary, **caused by low copper levels in soil and forages raised on that soil,** or
- secondary (**conditioned**), **when normal amounts of copper are present in soils and feeds but uptake and absorption are impeded by the presence of copper antagonists such as molybdenum, iron, manganese, cadmium, lead, and sulfates.**
- A genetic predisposition was postulated , Breed play a role in the disease in sheep, presumably through **differences in intestinal absorption and storage efficiency of copper.**

### **Pathogenesis**

- Copper is specifically **involved in myelination, osteogenesis, hematopoiesis, hair pigmentation, normal growth .**

- Copper plays an essential role in a number of **metabolic and developmental functions**, serving primarily in **tissue oxidation-phosphorylation reactions** as **part of the cytochrome oxidase system**.

The development of swayback, may be related to different and independent biological functions :

- a deficiency of cytochrome oxidase causing anorexia and chromatolysis in the neurons,- impaired phospholipid synthesis leading to impaired myelin synthesis,
- or a deficiency of dopamine-hydroxylase leading to an accumulation of catecholamines in the central nervous system .
- In congenital copper deficiency or **swayback**, severe, prolonged copper deficiency in the dam affects normal development of myelin throughout the entire CNS of the developing fetus. This form occurs frequently in lambs and is associated with cavitation lesions of the cerebrum.
- **Microcytic anemia and fragility of long bones** occasionally have been observed in **swayback kids**, reflecting the roles of copper in hematopoiesis and osteogenesis, respectively.
- **the postnatal disease enzootic ataxia** develops when copper deficiency occurs later in gestation, when the deficiency is less severe, or when the deficiency continues in offspring after birth.

### **Clinical Findings**

- Male and female kids of all breeds can be affected , -In congenital copper deficiency (swayback), kids are abnormal at birth and is a disease of un weaned lambs characterised by hindlimb inco-ordination.

-. They are weak and most are unable to rise unassisted, but may stand unsteadily if helped to their feet .

-Muscle tremors and persistent nodding or shaking of the head are characteristic

signs , Teeth grinding also occurs variably

--The predominant clinical sign is **swaying of the hindquarters** as the affected animal walks and this results in a stiff staggering gait. Such animals are bright, alert, able to suck , vocalize, see, and hear. and when lying down frequently appear normal. With intensive nursing care these kids may live from several days to several weeks.

-**In the delayed form of the disease, enzootic ataxia**, kids are born normally and develop a progressive paresis beginning as early as one week or as late as twenty-eight weeks of age.

A proportion of lambs are so ataxic at birth that they soon die while others appear normal and the condition develops gradually until walking is impossible.

- In mild cases ataxia may only become apparent when the lamb is excited or driven.,In multiple births it is common for all lambs to be affected but not necessarily to the same degree.

- The clinical course varies from one to fourteen weeks and at least in the early stages, kids remain bright and alert and continue to eat.
  - Early signs include **weakness, fatigue, tremors, difficulty in rising, and incoordination**. Symmetrical paresis and ataxia are usually observed first **in the hind limbs**, but sometimes in the forelimbs first. The signs are never unilateral.
  - Periodic spasmodic contractions of the hind limbs and overstretching of the tarsal joints may occur.
- Kids with forelimb involvement may drop onto their knees, while kids with hind limb involvement adopt a dog-sitting position and pull themselves along with the forelimbs
- Rising becomes progressively more difficult as paresis gives way to paralysis

Permanently recumbent kids show flexor contracture of the forelimbs, spastic extension of the hind limbs, decubital ulcers, and muscle wasting.Diarrhea may



,occur

Signs of copper deficiency in adults include ill thrift, diarrhea, anemia, and depigmentation of the hair coat

- **Diagnosis**

- Normal blood copper levels in goats are reported to be in the range of 9.4 to 23.6 mol/l (60 to 150 g/dl or **0.6 to 1.5 ppm**) .
- Blood or serum copper levels less than 8 mol/l (50g/dl or **0.5 ppm**) and liver copper levels less than **20 ppm** dry weight are reported to be diagnostic for enzootic ataxia.
- -A microcytic anemia may be seen in affected kids, and hemoglobin values in the range of (5 -7.7 g/dl ) have been reported .

## **necropsy**

1-Microscopic lesions are most common in the brain stem and spinal cord. The lesions are bilaterally symmetrical and are particularly obvious in the dorsolateral tracts of the cervical and thoracic spinal cord.

2- Neuronal degeneration and demyelination are characteristic.

Swelling of the neuronal cytoplasm with shrunken nuclei and marked chromatolysis is typical.

3- gliosis and phagocytosis are evident.

- **Differential diagnosis**

- includes hydrocephalus, congenital vertebra spinal abnormalities, caprine beta mannosidosis, border disease, hypoglycemia, and hypothermia.
- There is also a reported case of **granulomatous encephalitis in a newborn kid due to** congenital infection with ***Neospora caninum***, which produced signs similar to those of congenital copper deficiency
  - the neurologic form of CAE, **vertebral trauma, spinal abscesses, cerebrospinal nematodiasis, nutritional muscular dystrophy, floppy kid disease, and listeriosis** must be ruled out.

- In the early stages of disease, ascending paralysis caused by **rabies** is also a diagnostic consideration.

## Treatment

Because the lesions are irreversible treatment is of no value and severely affected lambs should be destroyed. Lambs suffering from a mild form of the disease may be fattened satisfactorily.

Mildly affected congenital cases, and early cases of enzootic ataxia, may respond favorably to treatment with copper compounds, but complete recovery is uncommon.

- **Copper glycinate** has been reported as an effective treatment given parenterally to kids as a single total dose of 60 mg .
- **Control**
  - -Effective control depends on determining the underlying cause of copper deficiency. **It may be necessary to assay feeds, water, and soils to ascertain if there is a primary copper deficiency or a secondary deficiency**
  - for sheep, copper levels in various feeds should be **at least 5 ppm and molybdenum levels should not exceed 5 ppm. The copper to molybdenum ratio in the overall diet should be kept between 5 : 1 and 10 : 1**
  - The current dietary copper recommendation for goats,, is 10 to 20 ppm.
- When soils are copper deficient, annual top-dressing of pasture with copper - .sulfate at a rate of 2 to 3 kg/ha is recommended

Enzootic ataxia may be prevented by supplementation of copper In the face of outbreaks of swayback or enzootic ataxia, pregnant does can be given copper glycinate s/c at a total dose of 150 mg at mid gestation to prevent subsequent .copper deficiency in kids

Kids can be given 60 mg of copper glycinate s/c at birth if does were not treated earlier in pregnancy. This should protect them at least through weaning.

- . **Oral copper sulfate in the drinking water of does at a dose of 1.5 g per head per**

week during pregnancy has also been used successfully, but may cause corrosion problems in metal pipes and troughs.

- Trace mineralized salts containing copper sulfate in the range of 0.5% to 2% can be made available in blocks free choice or incorporated into the concentrate ration.
- **A number of sustained release copper products for oral administration such as copper oxide needles in gelatin capsules have been used successfully in sheep in copper deficient areas,**

## **COPPER PREPARATIONS**

In sheep a number of injectable copper salts and ruminal boluses are available for the treatment and control of conditions related to copper deficiency. Care should be taken in the use of these products since some have higher toxicity risks than others.

The diagnosis of swayback is based on clinical signs and flock history of copper deficiency. However some of the clinical signs associated with spinal abscessation or border disease are similar, so liver copper assay and brain or spinal cord histopathology are often needed to support the diagnosis.

Soil and pasture copper concentrations alone are poor indices of deficiency, because most copper deficiency is induced by interfering factors. The interpretation of blood and liver copper concentrations is based on the following principles described

1. copper in excess of requirements is efficiently stored in the liver, which contains up to 70% of the total body copper reserves;
2. blood copper concentrations are maintained for as long as the liver stores are adequate;
3. when net copper absorption is insufficient to meet metabolic requirements, liver stores are mobilised to meet the shortfall;
4. the blood copper concentration remains constant until the liver becomes depleted;
5. blood copper concentrations fall only when the liver reserves are already

depleted and metabolic requirements continue to exceed net absorption .

6. clinical deficiency only occurs when the levels of copper at the essential sites fall  
There are four copper supplementation strategies:

**-Oral drenching with copper salts;**

**-Free access minerals,**

**-Copper injections and**

**- Copper capsules.**

The organic standards permit mineral supplementation of animals only where trace element requirements cannot be met by the practice of organic husbandry. Copper supplementation does not have to have prior approval, provided adequate justification can subsequently be shown.

The results of application of copper sulphate to pasture are very variable, and toxicosis is a hazard. It is therefore not a commonly used method and not recommended in organic farming.

Oral drenching with solutions containing 4 mmol (1 g) copper sulphate ( $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ ), given 8 and 4 weeks before lambing,

. This method, however, is not recommended in organic farming, as the handling involved is stressful for the pregnant ewes.

Copper treatments should also not be carried out at the same time as anthelmintics or if ewes are to be housed, as this can increase the risk of poisoning.

New-born lambs absorb copper up to 50 times more effectively than adult sheep, so the dose/unit body weight has to be reduced to  $25 \mu\text{mol}$  (6.25 mg)  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}/\text{kg}$  body weight, if they are to be dosed.

. The serum copper concentration in lambs less than 8 weeks old may not reflect the copper status of the flock

**-The use of copper oxide particles in capsules given orally is a popular conventional method.** The particles become lodged in the abomasum for several months and slowly release absorbable copper.

-Another popular method is the use of **slow release boluses** containing several minerals including copper. These slowly dissolve in the reticulo-rumen and release copper on a continuous basis. Slow release boluses are a useful method of copper supplementation for pregnant ewes.

-Pregnant ewes are sometimes injected with commercial copper preparations based on the presence of hypocupraemia (plasma copper  $<9.42 \mu\text{mol}$  (0.6 mg)/l) to prevent swayback

## General Treatment and control

Treatment of copper-deficient animals is usually possible, and the prognosis is guarded to good, depending on the severity of the lesions.

- When excess molybdenum, sulfate, and other factors leading to secondary deficiency are present, they can be overcome to some extent by increasing dietary copper or by injecting copper.

-Injectable copper glycinate (30% copper by weight) is given to adult cattle at the rate of 400mg (120 mg copper) subcutaneously.

- Calves are given 100 to 200 mg of copper glycinate (30 to 60 mg of copper), depending upon their age.

-One injection may be effective as a treatment/supplement for up to 4 to 6 months in cases of primary copper deficiency.

However, in cases of excess molybdenum, sulfates, and/or sulfur, repeat injections may be necessary.

-Injections of copper glycinate frequently result in large swellings, granulomas, or abscesses and may be cosmetic considerations for some cattle. The reactions can be minimized by using sterile technique and using the subcutaneous tissue of the brisket as the injection site.

- Copper can be supplemented to cattle in salt-mineral mixes in situations in which adequate consumption [28 to 56 g/cow/day) of the salt-mineral mix occurs. These mixes are usually 0.2 to 0.6% copper.

- Feed grade copper sulfate ( $\text{CuSO}_4 \cdot 5 \text{H}_2\text{O}$ ) is copper on an as fed basis (40% copper on dry matter basis).

-Feed grade copper oxide is usually copper as fed (80% copper on a 100% dry matter basis). To make a 0.4% copper salt mixture, add 7.2 g of  $\text{CuSO}_4$  or 3.6 g of  $\text{CuO}$  to each 454 g of salt.

-Salt mixtures for sheep should usually contain only copper (0.25% to 0.5% copper sulfate). Copper supplements can be added to a total mixed ration

easily in the form of trace mineral-vitamin premixes or premix-containing pellets.

Copper sulfate can be added to molasses or other sweet feed at 0.363 g/head/day for mature cattle and correspondingly less for calves.

-The copper in  $\text{CuSO}_4$  is more available than that in  $\text{CuO}$ . In some countries copper EDTA (copper disodium edetate) solutions are used as injectable copper supplements. The dosage of copper is usually the same as that recommended for copper glycinate solutions. However, acute deaths can occur following its use in cattle.

- Another method of copper supplementation involves the oral administration of copper Oxide needles (fine rods, 1 to 10 mm long) placed in gelatin capsules which dissolve in the reticulo-rumen and liberate the  $\text{CuO}$  wires. These wires reside in the reticulum and abomasum and slowly release copper for absorption. These boluses are currently available in the U.S.

**- One 12.5 g bolus is recommended for calves and the usual dose is 2 to 4 g for ewes and does, which is an extra label recommendation for sheep and goats.**

**--The copper oxide needles are thought to provide copper supplementation for 4 to 12 months.**

Sheep are particularly susceptible to copper toxicity, and appropriate care is necessary when supplementing them.

- Continued monitoring of hepatic copper concentration from slaughtered animals is an important tool in evaluating copper supplementation methods in cattle and sheep.

- Lambs can be given 35 mg of copper sulfate per head twice weekly to prevent swayback in endemic areas.

-The usual recommendation by the National Research Council is 10 ppm (10 mg/kg) of the total diet on a dry matter basis (DMB) for cattle. However, diets of 20 ppm are commonly fed to lactating dairy cattle.

-The most important goal of copper supplementation is to provide adequate dietary amounts without over supplementing or risking toxicity.