Copper and animal health: Importance, maternal fetal, immunity and DNA relationship, deficiency and toxicity

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Abstract
Copper is an important trace element that plays a very important role in the biochemistry of all living organisms and affects enzymes activity as a cofactor or as a fundamental structure of many metalloenzymes as superoxide dismutase, ceruloplasmin, lysyl oxidase, cytochrome oxidase and tyrosinase. Therefore copper is essential for cellular respiration, free radical defence, neurotransmitter function connective and tissue biosynthesis. Excessive copper accumulation is toxic in all species as it leads to hepatic cirrhosis, hemolytic anemia and degeneration of basal ganglia. The aim of this review is to give a view on the health issue surrounding copper and animal health including many interested points about copper and fetal maternal relationship, the role of copper in the different body system and the effect of its deficiency and toxicity, as well as focusing on the relationship of copper with other trace elements, metalloenzymes, immunity and DNA.

Key words: Copper, animal, health

Introduction
Copper is an essential trace element for all biological organisms, from bacterial cells to human. Depending on the source of the biological material, copper content ranges from parts per billion to parts per million. Copper deficiency has been linked to a variety to clinical signs, including pale coat, poor sheep fleece quality, anaemia, spontaneous fractures, poor capillary integrity, myocardial degeneration, hypomyelination of the spinal cord, impaired reproductive performance, decreased resistance to infectious disease, diarrhoea and generalized ill-health (1), causing sever economic losses. Hypocuprosis is the second most widespread mineral deficiency affecting grazing animals, many investigations concerning the mechanisms of copper activity in the body have dealt primarily with the distribution of copper in various tissues, the changes which occur in the blood after different conditions and the interrelationships between copper and various enzymes systems, vitamins and minerals.

(2) explained that Cu is an essential trace element that has an important role in many physiological functions in nervous, hematological, cardiovascular, reproduction and immune systems. Moreover, Cu plays a significant role, being associated with specific proteins. The majority of the biological functions of Cu are believed to be associated with copper’s role as a ligand in the active site of metalloenzymes. Among the principal enzymes, ceruloplasmin (a plasma glyco-protein, may function as a Cu transport and as an antioxidant), Dopamine-β-monoxygenase (located in noradrenergic neurons and involved in conversion of dopamine to norepinephrine), Cytochrome-c-oxidase (the terminal mitochondrial electron carrier), lysyl oxidase (responsible for oxidative deamination of peptidyl lysine), Cu-Zn-Superoxide dismutase (a cytosolic protein that speeds up the dismutation of superoxide) and
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Tyrosinase (located in melanocytes and involved in the conversion of tyrosine into melanin) and Cu is needed for proper development of antibodies and white blood cells in addition to antioxidant enzyme production(3). Cu deficient goats are more susceptible to infections and do not respond as well to vaccinations. In addition, they tend to be less resistant to parasitic challenge. Goats receiving proper Cu nutrition tend to be less susceptible to infections and have less severe infections when disease does occur.

The focus of this review article is the health issue surrounding copper and animal health including many interested points about copper and fetal maternal relationship, the role of copper in the different body system and the effect of its deficiency, toxicity and supplementaton , as well as focusing on the relationship of copper with other trace elements, metalloenzymes, immunity and DNA.

Copper and metalloenzymes

Copper is essential both for its role in antioxidant enzymes, like Cu/zinc superoxide dismutase and ceruloplasmin, as well as its role in lysyl oxidase, essential for the strength and integrity of the heart and blood vessels. With such a central role in cardiovascular health, Cu has been generally overlooked in the debate over improving our cardiovascular health. Cu deficiency has produced many of the same abnormalities present in cardiovascular disease. It seems almost certain that Cu plays a large role in the development of this killer disease, not because of its excess in the diet, but rather its deficiency (4).

The biochemical role for copper is primarily catalytic, with many copper metalloenzymes acting as oxidases to achieve the reduction of molecular oxygen. Many copper metalloenzymes have been identified (5). Diamine oxidase inactivates histamine release during allergic reaction, monoamine oxidase is important in serotonin degradation to escretable metabolites and in the metabolism of catecholamines (epinephrine, norepinephrine and dopamin), lysyle oxidase uses lysine and hydroxylysine found in collagen and elastin as substrates for posttransational process to produce cross-linkage needed for the development of connective tissues including those of bone, lung and the circulatory system as well as lysyl oxidase activity in the skin, which declined with low dietary copper and increased with repletion, is potentially a useful indicator of copper status.

Copper is an essential part of ferroxidases enzymes found in plasma (6), with a function in ferrus ion oxidation that is needed to achieve iron’s binding to transferrin. Ferroxidase I, also called ceruloplasmin, is the predominant copper protein in plasma and may also have antioxidant functions. Defects in ceruloplasmin function produce cellular iron accumulation, a result that support its ferroxidase role (5). Ceruloplasmin concentration is also a reliable indicator of copper deficiency as it carries between 60-95 percent of serum copper, and changes in serum copper concentration usually parallel the ceruloplasmin concentration in the blood (7). Each molecule of ceruloplasmin contains six to eight atoms of copper which influence its biological activity and it have been isolated from several animal species including man and have a similar chemical structure (8), biochemical properties of ceruloplasmin such as optimal pH are often similar in various animal species.

The impact of copper deficiency on the antioxidant system and oxidative damage of cellular components has been reported in several species and tissues, as well as in cultured cells. Ceruloplasmin is the main cupremic determinant and appears to be one of the enzymes most sensitive to copper deficiency (9). In this sense, it is well known that low Ceruloplasmin levels are related to an increased susceptibility to infections and tissue injuries. It has been suggested that Ceruloplasmin in plasma acts as an extracellular scavenger of free radicals and may thus protect the cells against reactive oxygen species released from neutrophils and macrophages (10).

In domestic animals, ceruloplasmin has been used diagnostically to investigate copper deficiency (11). Animals treated with copper preparations show increased ceruloplasmin activity (12) and blood
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copper concentrations, however a number of variables must be considered to fully evaluate the copper status. Similar correlations between ceruloplasmin and blood copper concentrations have been reported by other investigators as well as ceruloplasmin appears to be a useful indicator of nutritional copper status in cattle and sheep. Ceruloplasmin activity and the serum or plasma copper concentration decreases with nutritional copper depletion of cattle (13).

In cattle, correlation coefficients as high as 0.93 have been observed using plasma samples while in sheep, comparisons between serum ceruloplasmin and whole blood copper concentrations have also produced good correlations (r = 0.75) and since ceruloplasmin is reported to contain greater than 95% of the circulating copper in normal animal (14), ceruloplasmin synthesis occurs in the liver, a major site of copper storage, it could be expected that ceruloplasmin activity would be a useful indicator of hepatic copper concentrations. Plasma has more ceruloplasmin activity than serum, suggesting a relatively greater sequestration of ceruloplasmin than copper during the clotting process. Under routine diagnostic laboratory conditions, ceruloplasmin appears to be a useful diagnostic aid to evaluate copper status in cattle and sheep. Ceruloplasmin may function as an antioxidant in two different ways: by binding to Cu, ceruloplasmin prevents free Cu ions from catalyzing oxidative damage. The other way is through the oxidation of ferrous iron by ceruloplasmin, facilitating iron load into its transport protein, transferrin, and preventing free ferrous ions from participating in harmful free radical generating reactions (4).

Two forms of superoxide dismutase are expressed in mammalian cells, a manganese and copper/zinc form (4,14). Copper/zinc superoxide dismutase uses two copper atoms for conversion of the superoxide anion (O_2^-) to H_2O_2 and O_2. There is substantial documentation from animal studies that diets low in copper reduce the activities of many of these copper metalloenzymes. Activities of some copper metalloenzymes have been shown to decrease in copper depletion. Erythrocyte superoxide dismutase activity, though not as specific as serum copper or ceruloplasmin concentration, may be a reliable indicator of copper status, and some suggest it is more sensitive.

The consequences of hypocuprosis include a failure of copper metalloenzymes many of which form part of the antioxidant defence system. Copper is associated with several enzymes, either as a cofactor or as an allosteric component. Copper acts as an electron transfer intermediate in redox reactions, being an essential cofactor for oxidative and reductase enzymes (15). The consequences of hypocuprosis include a failure of copper metalloenzymes, many of which form part of the antioxidant defence system as Copper/Zinc superoxide dismutase and caeruloplasmin. Copper, as well as other essential trace elements, is an atypical antioxidant because it works indirectly. Copper is a catalytic cofactor for Copper/Zinc superoxide dismutase and caeruloplasmin. Copper/Zinc superoxide dismutase catalyzes dismutation of the superoxide anion, producing molecular oxygen and hydrogen peroxide, with the latter product usually metabolized by glutathione peroxidase and catalase. The ferroxidase activity of caeruloplasmin mediates the oxidation of ferrous ions to the ferric state, thereby preventing ferrous ion-dependent formation of hydroxyl radicals via the Fenton reaction. Thus, in enabling Copper/Zinc superoxide dismutase and caeruloplasmin to function, copper can be classified as part of the antioxidant defence system of cells (16). The impact of copper deficiency on the antioxidant defence system and oxidative damage to cellular components. The activity of Copper/Zinc Superoxide dismutase, catalase and glutathione peroxidase is decreased in animals with copper deficiency and increased in animal with copper supplementation (17). Machado et al. (18) found that supplementation with trace mineral containing copper increased serum superoxide dismutase activities in lactating Holstein cows.

Cattle hypocuprosis was associated with a decrease in Copper/Zinc Superoxide dismutase, ceruloplasmin and cytochrom oxidase activity and with an increase in lipid peroxidation (10).
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Collectively, these studies indicate that copper deficiency weakens the antioxidant defense mechanism. Several enzymes with antioxidant activity which do not require copper as a cofactor, such as catalase and glutathione peroxidase, are known to be negatively influenced by copper deficiency, increasing free radicals generated in the cells. Cu deficiency impairs secretion of tyrosine hydroxylase and dopamine beta enzyme systems, which are both Cu-containing in hypothalamic neurons. This causes inhibition of synthesis of thyroid hormone-releasing factor (19). Soetan et al. (20) demonstrated that Cu is a constituent of enzymes like cytochrome-c-oxidase, amineoxidase, catalase, peroxidase, ascorbic acid oxidase, plasma monoamine oxidase, erythrocuprin (ceruloplasmin), lactase, uricase, tyrosinase, cytosolic superoxide dismutase. Moreover, it is necessary for the growth and formation of bone, formation of myelin sheaths in the nervous systems, helps in the incorporation of iron in haemoglobin, assists in the absorption of iron from the gastrointestinal tract and in the transfer of iron from tissues to the plasma. Fry (21) demonstrated that Cu is required for the activity of superoxide dismutase and that two Cu+ ions are bound to the enzyme. This enzyme is responsible for the reduction of the superoxide to hydrogen peroxide and oxygen in the cell.

Copper and immunity

Copper is known to play an important role in development and maintenance of the immune system which requires copper to perform several functions, of which little is known about the direct mechanism of action. There are several reports of dysfunction in vitro in immune cells from copper-deficient ruminants. The ability of peripheral blood granulocytes from copper-deficient sheep and cattle to ingest Candida albicans in vitro may (22) or may not be impaired, but their capacity to kill the engulfed organism is invariably reduced (23). Both deficiency and excessive intake of copper have been reported to reduce several aspects of immune response in animal models, including neutrophil numbers and its phagocytic activity (24), lymphocyte proliferation, and antigen-specific antibody production (25). Treated calves with Cu had increased neutrophil activity compared with non-treated calves (26) while (27) found that Cu supplemented lactating Holstein cow had significant increased serum superoxide dismutase activity although leukocyte function was not affected by supplementation.

Copper deficiency, in general, reduces the effectiveness of the acquired response (28). Early studies of copper deficiency, in which ceruloplasmin was almost nondetectable, determined that the copper-deficient animals were anemic, their thymus weights were significantly lower, and their spleen weights were significantly higher than in normal animals as well as antibody production was significantly reduced in copper-deficient animals(29). Splenocytes in copper-deficient animals had a reduction in the incorporation of tritiated thymidine into cellular DNA in a standard mitogenic proliferation assay and the mitogen-induced synthesis of DNA was impaired by copper deficiency (30).

Copper also is utilized in host immune systems to prevent infection, not only is copper required for proper development of the immune system (31), but also, new evidence shows that copper is employed at a cellular level to kill invading bacteria (32). Copper accumulates in granulomas of guinea pigs infected with Mycobacterium tuberculosis and that copper resistance is required for full virulence in Mycobacterium tuberculosis (33). Multicopper oxidases play a crucial role in copper detoxification in many bacteria, including Escherichia coli (34), Pseudomonas syringae and Salmonella enterica (35).

Reductions in Superoxide dismutase activity in leucocytes from copper-deficient sheep accompanied increased release of Superoxide anion, suggesting that superoxide might accumulate and weaken the phagocyte after the pathogen triggers the respiratory burst (23). However, in cells from the copper-deficient bovine, candidacidal activity is reduced before leukocyte superoxide dismutase activity
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decreases, while decreased nitro blue tetrazolium reduction indicates lowered intracellular concentration of Superoxide anion (22).

The physiological role of Superoxide may vary between species and with the severity of copper deficiency, while Copper is an appropriate element with which to begin, since it has been clearly shown to influence resistance of sheep to bacterial infections (22). The Scottish Blackface hill breed, which was naturally susceptible to copper deficiency, and a line selected for low plasma copper both produced lambs that were highly vulnerable to microbial infections when pasture improvement by liming and reseeding lowered their copper status. The susceptible genotypes were protected by copper supplementation.

Schuschke et al. (36) found an increase in the mast cell population in the cremaster muscle of copper-deficient animals, suggesting that copper deficiency might alter the distribution of blood cells into tissues or the maturation patterns of the leukocyte population. Copper supplementation influences the resistance of ruminants to viral infection as bovine herpes virus -1(37) rift valley virus (38) and Haemonchus contortus infection in lambs as it reduced egg per gram feces in copper supplemented lambs (39) and goat (40) while Schafer et al. (41) found that, copper supplementation enhancing the immune response in lambs experimentally infected with Haemonchus contortus. However, it did not reduce egg counts in the feces or the number of adult parasites in the abomasum. Copper supplementation decreased antibiotic resistance of E-coli in pigs(42) and in dairy cows (43), increased colostrum immunoglobulins and decreased calve mortality during calving specially when it was supplemented in the form of organic trace minerals (44). Sharma et al. (19) stated that the antimicrobial activity of the neutrophils from Cu-deficient calves decreased compared with neutrophils from Cu supplemented calves. Zhou et al. (45) mentioned that ruminants with Cu deficiency have lower lymphocytes percentages than normal and tend to have decreased cytokine responses to disease challenge.

Copper and maternal fetal relationship
Pregnancy is a period of rapid growth and cell differentiation for both the mother and fetus. Consequently, it is a period when both are vulnerable to changes in dietary supply, especially of those nutrients that are marginal under normal circumstances (46). Each fetus is completely dependent on its dam via the placenta for its supply of essential trace elements (47), but embryo quality not affected by copper supplementation during the gestational period in cattle (48). Copper is often one of the most limiting trace elements for the fetus and neonate for normal development and copper play a major etiologic role in decrease of fetal growth and development (49). Deficiency of copper impairs fetal growth and causes serious consequences (50) and can cause death. Calves normally are born with liver Cu concentrations of approximately 400 ppm, compared with adult concentrations of 200 ppm (51). When intakes of Cu are deficient, maternal transfer of Cu to the fetus is insufficient for normal development, and abnormalities to the central nervous system (52), skeleton, and metabolism result.

It was reported that there is extraordinary metabolic demands on both the mother and developing fetus associated with gestation because adequate maternal copper nutritive is essential for normal embryogenesis (53). Copper is an essential trace element that plays an important role in the biochemical reactions of the body; however, its requirement and interaction with other minerals is not clearly understood (54). Hepatic concentrations of trace elements are commonly used to estimate trace element storage pools because dietary intake is rarely available and nutrient interactions affect availability or retention (55).

Maternal liver Cu was negatively correlated with fetal age, (56) while, Graham et al. (57) found that maternal liver Cu was not correlated with fetal size. Fetal liver Cu increased as fetal age increased and was less than to maternal Cu in early gestation and there was no differences between maternal and

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fetal liver Cu in late gestation, while Gonneratne and Christensen (58) found that, fetal liver Cu was significantly higher than that of the maternal liver through gestation, as well as Cu concentration was significantly increased in early gestation than that of late gestation in the fetal liver and kidney (47) while Richards (59) found that in fetal kidney, Cu concentration did not change significantly with gestation.

Because copper is essential for development of the central nervous system of the embryonic lamb, an acute maternal hypocuprosis can cause gross brain lesions in the fetal or neonate lamb (60). Ovine maternal and fetal liver Cu were negatively correlated in this and previous reports (58). Presence of significant negative relationship between age of the fetus and maternal liver Cu concentration as well as the relationships between maternal liver and amniotic and allantoic fluid Cu concentrations were significantly negative, while the relationship between age of the fetus and maternal plasma, fetal liver, amniotic fluid, allantoic fluid and fetal kidney Cu concentrations were significantly positive may indicate that, the dam and fetus depend on the maternal liver Cu contents during gestation (56) and liver copper can be used as an indicator of the Cu status (61) through gestation and fetuses have a capacity to sequester maternal Cu, even when the dam is Cu deficient (57). Parkinson (62) found that amniotic fluid copper concentration gradually increased during pregnancy

Adequate maternal intake of Cu is essential for development of the central nervous system (CNS) of the embryonic lamb. Consequences of Cu deficiency during intrauterine life may include gross brain lesions, with affected lambs born dead or dying shortly after birth. Enzootic ataxia of the unborn or the unweaned lamb is primarily from Cu deficiency (60) a degeneration of myelin in the spinal cord being responsible for the ataxia that frequently affects the hind limbs. Histologically, the pathological process of enzootic ataxia of lambs suggests a disorder of nervous parenchyma in myelination areas in the form of a spongy inhibition associated with functional vascular disorders . Ewes deficient in copper give birth to lambs characterized by a partial herniation of the cerebellum such that anteriorly the fissura prima lay beneath the tentorium cerebelli and posteriorly formed a "tail" in the foramen magnum (63). Lesions in the brain and spinal cord characteristic of enzootic ataxia could be detected as early as 99 days postconception in fetal lambs whose dams were grazing on land where enzootic ataxia (swayback) occurred . However, the characteristic lesion of delayed swayback is not present at birth but develops in the postnatal period (60).

Administration of therapeutically effective amounts of copper to the ewe could be delayed until the last month of pregnancy and still be effective in preventing swayback in the offspring . It appears that an inadequate supply of copper to the fetus during the last 3 or 4 wk of gestation can cause swayback. In guinea pigs deficient of Cu that showed gross brain changes at birth, it was postulated that the supply of copper was inadequate during fetal development to maintain the necessary oxidase activity. Moreover, the deficiency of copper also might limit synthesis of phospholipid (60).

Because of high demand for copper for the developing embryo, the Cu-deficient ewe is unable, apparently, to maintain a Cu reserve adequate for normal functional purposes during late gestation. However, in some cases Cu-deficient ewes give birth to an unaffected lamb; in these ewes more Cu crosses the placenta than in the ewe giving birth to an affected lamb. There is constant increase in copper deposition throughout the fetal period and, therefore, an increasing demand for copper by the fetus. The pregnant ewe appears to be equipped poorly to protect her lamb against effects of a dietary deficiency of copper. Her blood and plasma copper falls during pregnancy and again after parturition, perhaps from the physiological disturbances that accompany pregnancy, such as an increase in blood volume and demands of the developing fetus (56).
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When Cu is absorbed by the ewe, it is transferred to the liver and converted into hepatocuprein and then into haemocuprein for liberation into the blood stream. It may be that the hepatocuprein or other Cu complexes in the liver govern transfer of Cu from dam to fetus. The concentration of Cu in the mammalian liver is higher at birth than at any other time during life. More than 50% of the total Cu in the body of most newborn lambs is in the liver (64). Much of the copper in fetal bovine liver is in the mitochondria as a copper-protein complex called neonatal hepatic mitochondrocuprein, which contains about 40 mg Cu/kg (57,60). Between 15 and 35% of the total hepatic Cu of the sheep fetus, corresponding to most of the cytosol Cu, is in the metallothionein-containing fraction. Copper concentrations in liver increased towards the end of gestation in ewes. (56). Liver Cu begins to decrease soon after birth, presumably from mobilization to meet the needs of other tissues of the growing animal. The substantial store of Cu in the liver of newborn animals would be of advantage when the sole source of exogenous Cu is milk, which is usually low in copper (60).

Copper deficiency during embryonic and fetal development can result in numerous gross structural and biochemical abnormalities. Such a deficiency can arise through a variety of mechanisms, including low maternal dietary copper intake, disease-induced or drug-induced changes in maternal and conceptus copper metabolism, or both (53). High copper content in most newborn animals has suggested placental transfer and storage before birth.

Copper and DNA

Pan and Loo (16) showed an increase in DNA damage measured by the comet assay in Jurkat T lymphocytes cultured with the copper chelator 2,3,2-tetramine after exposure to hydrogen peroxide. Copper levels are necessary to maintain the structural integrity of DNA during oxidative stress as copper has essential role of inhibition of oxidative damage of DNA (65,66). However, Cu deficiency in Jurkat T lymphocytes itself did not have genotoxic effects and the increase of DNA damage and an increase in the frequency of chromosomal aberrations found in hypocupremic animals could be explained by higher oxidative stress suffered by these animals (10). In Cu-deficient rat embryos a tendency to higher 8-hydroxy-2-deoxyguanosine concentrations was observed by (67). As well as a clear relationship between copper deficiency and the yield of DNA damage was observed by (10).

Excess copper can be lethal which acts predominantly through formation of highly reactive hydroxyl radicals by Fenton type reaction which damages DNA and other macromolecules (68), further studies also found that in chromatin isolated from frozen calf thymus has been reported to contain 25ng of tightly bound copper while (69) reported that there is an average of one copper atom bound for every two nucleotides equivalent to 1.2µmol/mg of double DNA as well as (70) concluded that direct interaction of transitional metal (copper) to DNA in the presence of hydrogen peroxide caused destabilization and fragmentation of chromatin structure i.e. when DNA was not protected within a nuclear cellular milieu, nucleotides bases were more prone to interact with transitional metal (copper) and caused DNA fragmentation. (Linder (71)) cited that studies of the structural integrity of the nuclear matrix associated with chromosomal DNA indicated that Cu ions are important for maintaining at least one level of folding of the DNA strands. Moreover, it is clear that nuclei contain a significant proportion of cellular Cu and that much of that is actually bound to DNA bases. Goats with experimentally-induced copper deficiency have DNA fragmentation as detected by gel electrophoresis and the DNA ladder represented a series of fragments that is multiples of 180–200 bp. which suggest a significant role of copper deficiency in induction of DNA damage and cell apoptosis in goats (38).

Copper deficiency
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Physiologic consequences resulting from copper deficiency include defects in connective tissue that lead to vascular and skeletal problems, anemia associated with defective iron utilization, and possibly specific aspects of central nervous system dysfunction. Some evidence suggests that immune and cardiac dysfunction occurs in experimental copper deficiency and the development of such signs of deficiency has been demonstrated in infants. Copper deficiency causes a disease in lambs called enzootic ataxia (also known as swayback). This disorder, is characterized by spastic paralysis (especially of the hind limbs), severe uncoordination, and anemia. The brains of affected animals are typically smaller than normal, have collapsed cerebral hemispheres and shallow convolutions, and are hypomyelinated (53).

Clinical symptoms of Cu deficiency vary and include poor appetite in congenital forms, weakness of limbs, twisted joints, edema, head tremors, incoordination, ataxia, paresis, and paralysis (72), osteochondrosis (73), poor body condition, growth rate, and coats. Degeneration and necrosis of the motor neurons in the medulla spinalis and cerebellum as well as demyelination were also reported in cases of Cu deficiency (74). Copper deficiency is clearly teratogenic and also induces adverse developmental and neurobehavioral effects. The nature and magnitude of these effects depend on (a) timing of copper deficiency during reproduction and development, (b) extent of copper deficiency, and (c) animal species (75). The major target organs for copper deficiency are the blood and hematopoietic system, the cardiovascular system, connective tissue and bone, the nervous system, and the immune system (76). Reported adverse effects of copper deficiency include anemia, decreased erythropoiesis and altered hematology, impaired immune function and neurological development, altered cardiac function and lipid metabolism were recorded by further researches.

Copper is important for thyroid hormones due to its role in synthesis or conversion of thyroid hormones (52,77). Copper deficiency impairs secretion of tyrosine hydroxylase and dopamine beta enzymes which are both containing, in the hypothalamic neurons, this causes inhibition of synthesis of thyroid hormone releasing factor (24), so copper deficiency may have effect on the sexual development and spermatogenesis. In female rats, severe copper deficiency during gestation induces fetal resorptions or stillbirths. The offspring of pregnant rats given a copper-deficient diet during gestation have increased postnatal mortality and a high incidence of structural and behavioral abnormalities, including brain lesions, skeletal malformations, cardiovascular lesions, severe growth retardation, convulsions, and hyperirritability to noise. Low copper levels in cattle can result in many problems from poor hair coat to reduced weight gains, impaired immune system, broken bones, or lower reproduction rates (78). When deficiency is corrected, they do better.

One of the most visible signs of copper deficiency is change in hair color. Black animals develop a red tint and red animals become bleached and light colored. The coat becomes dull and animals may be slow to shed in the spring. In young animals, copper deficiency can result in diarrhea (79) and higher incidence of diseases, lameness, and poor response to vaccination. Affected animals may have a stiff gait; the ends of the cannon bones may be enlarged and painful, with sore fetlock joints. Pasterns may be upright, with the calf walking on its toes. Bones may be weak and brittle. Heifers may be late reaching puberty and fertility may be impaired. Cows may be slow to cycle after calving. Cattle may develop severe copper deficiency due to excess of other trace minerals such as molybdenum or sulfur. Deficiency may be primary when there’s not enough copper in the soil or plants grown on those soils, or secondary when other factors prevent utilization of copper. Elements that bind with copper to prevent absorption by the body include molybdenum, iron, zinc, sulfur, lead and calcium carbonate.

Cu deficiency has been linked to a variety of clinical signs, including pale coat, poor sheep fleece quality, anaemia (80), spontaneous fractures, poor capillary integrity, myocardial degeneration,
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hypomyelinization of the spinal cord, impaired reproductive performance, decreased resistance to infectious disease, diarrhea and generalized ill-health causing severe economic losses. Cu-deficiency in cattle include poor weight gain/weight loss, poor hair coat, pale mucous membranes, anemia, and neonatal ataxia (81) and impaired reproductive functions, alterations in cardiac function, anaemia and fragile bones. Ozkul et al. (72) observed that clinical symptoms of congenital Cu deficiency include poor appetite, weakness of limbs, twisted joints, edema, head tremors, incoordination, ataxia, paresis, and paralysis.

Cu (Cu) deficiency during pregnancy can result in early embryonic death and gross structural abnormalities in the embryo and fetus, including skeletal, neuronal, pulmonary, and cardiovascular defects. Morphologically, the Cu-deficient embryos were characterized by blisters, blood pooling, heart anomalies, and swollen hindbrain (67). Swayback disease is caused by Cu deficiency and it affects several species of domestic and wild animals. Clinical signs in animals include decreased growth rate, anemia, ataxia, bone disorders, diarrhea, abnormal pigmentation (3,82), and poor reproductive performance. The clinical disease is affected by several factors, including the species, age, and sex of the affected animals, and the duration and severity of the Cu deficiency; ruminants are the species most highly susceptible to Cu deficiency (83).

Legleiter and Spears (84) reported that Cu deficiency in the bovine, a widespread problem in many areas, may result in decreased growth, anemia, weak bones, cardiac failure, depigmentation of hair, and reduced reproductive efficiency. Handeland et al. (85) stated that Cu (Cu) deficiency causes various disease syndromes in ruminants. Cu deficiency has been associated with general unthrift, recognized as poor body condition, growth rates and coats, as well as enzootic ataxia and osteochondrosis. Sharma et al. (19) founded that the Cu-deficient animals were listless, showed depigmentation of the skin and stiff gait and were anemic and diarrheic. Moreover, the serum haemoglobin values in Cu-deficient animals were significantly lower than in the animals on Cu-rich diet.

Shalaby et al. (86) mentioned that the wool of Cu deficiency sheep loses its crimp and become steely, the fact that steely wool has more sulphahydryl groups (SH) and fewer disulphide group (S-S) suggests that Cu required for the oxidation of SH to S-S groups in keratin synthesis. Soetan et al. (20) stated that clinical disorders associated with Cu deficiencies include anaemia, bone disorders, neonatal ataxia, depigmentation and abnormal growth of hair or wool, impaired growth and reproductive performance, heart failure and gastrointestinal disturbances.

Copper toxicity

The importance of copper (Cu) in animal health and disease is well documented. Both Cu deficiency and Cu toxicity can occur in natural conditions and may lead to diminished animal production, reproduction (78), various organs dysfunctions (87), development of pathological lesions and, ultimately, to death of the animal. Cu toxicity is caused by an unbalance between the influx of Cu into the body and the excretion of Cu from the body, leading to accumulation of Cu in the liver with consequent liver cell damage. This imbalance may be due to an increased dietary supply of Cu, to an increased availability of the ingested Cu, or to a decreased biliary excretion of Cu. The diagnosis of Cu toxicity was based on toxicological analysis of biological, plant, and soil samples as well as the supportive medical history, clinical signs, necropsy lesions, liver (88) and kidney concentrations of copper (89) and microscopic findings in sections of liver.

There are two forms of copper poisoning – acute and chronic. Acute copper poisoning can result from the accidental administration of large quantities of copper (often via oral copper salts, parenteral copper administration, or grazing pasture recently fertilised with copper) (90). Chronic copper poisoning
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is associated with the slow accumulation in the liver of smaller amounts of copper ingested over a long period of time, but with no change in blood copper levels. When the liver’s capacity to accumulate copper is overloaded, usually after a stressful event, there is a release of copper into the bloodstream that leads to intravascular haemolysis. Combined with liver damage this causes acute toxicosis and recumbency with affected animals often dying within 24-48 hours; these animals show symptoms of profound depression, thirst, anorexia, pale or icteric mucus membranes and haemoglobinuria (61).

Copper is a well-documented cause of liver toxicity in many domestic species, including sheep, dogs, cats, horses, cattle, goats, pigs, and camelids (91,92). Sheep is the most sensitive domestic animal to copper toxicity because their Cu excretory mechanism is less efficient. Acute Cu toxicity is usually seen after accidental administration of excessive amounts of soluble Cu salts, which may be present in anthelmintic drenches, mineral mixes, or improperly formulated rations. In most cases, sheep undergo chronic exposure to copper causing liver necrosis and resulting in massive haemolysis, haemoglobinuria and eventually in renal failure (93). Sheep are more susceptible to the effects of Cu toxicity than other species of farm animals.

There are 3 main causes of hepatic copper accumulation: excessive dietary copper, inherent defects in copper metabolism, or impaired copper excretion in bile. Excessive gastrointestinal copper absorption may exceed the metabolic capacity for storage in the liver (89), this is the chief mode of copper toxicity in sheep on pastures rich in copper-containing plants or deficient in molybdenum (94). In domestic animals, most cases of acute copper toxicity result from the parenteral administration of copper-containing compounds (copper glycinate) or the consumption of copper sulfate–containing footbaths, licks, or salt-mineral mixes (95).

Liver damage is an important feature of all Cu storage diseases. The toxicity of Cu has been demonstrated in in vitro studies and is mainly derived from its ability to bind to sulphhydryl groups, nucleic acids, and tubulin, thus impairing such cellular functions as enzyme activity, protein synthesis, and intracellular transport. The elevated blood Cu leads to erythrocyte damage, methaemoglobin production, and Heinz body formation with subsequent haemolysis. According to (96) the possible causes of haemolysis of erythrocytes are three alternative mechanisms: decreased red cell deformability due to Heinzbody formation, chemical and/or mechanical changes in red cell membranes due to Heinz body attachment, and direct oxidative injury to the red cell membrane. Although in his view Heinz body formation may be the principal cause, evidence is available suggesting that Cu may cause lipid peroxidation in the erythrocyte membrane, leading to its disruption (97), this process may somehow be related to an inhibition of glycolytic enzymes and a concomitant decrease of the glutathione concentration in the erythrocyte and decrease the activity of glucose-6-phosphate dehydrogenase (98).

When Cu is ingested in large amounts in the diet, it may accumulate within the liver over a period of a few weeks to more than a year without clinical signs followed by a sudden release of liver Cu stores with resultant toxicity. Many factors that alter Cu metabolism can influence chronic Cu toxicity by enhancing the absorption or retention of Cu. Chronic Cu toxicity may result from excessive intake of Cu; low intake of molybdenum, sulphur, zinc, or calcium; or liver damage (82). In Cu toxicity, blood Cu concentrations may increase suddenly, causing lipid peroxidation and intravascular hemolysis.

Acute toxicity may follow ingestion of 20 to 100 mg of Cu/kg body weight in sheep, while chronic toxicity of sheep may occur with daily intake of 3.5 mg of Cu/kg body weight when grazing pastures that contain 15–20 mg of Cu/kg on a dry weight basis with concurrent low concentrations of molybdenum and sulfur (94) and chronic copper toxicity was appeared when copper supplementation was 2mg copper/kg body weigh daily for 105 days in cattle and buffalos (88). Acute Cu toxicity causes
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severe gastroenteritis with abomasal erosions and ulcerations, abdominal pain, diarrhea, anorexia, dehydration, and shock.

Hemolysis and hemoglobinuria may develop after 3 days if the animal survives these gastrointestinal disturbances. Icterus usually develops in animals that survive more than 24 hr. The sudden onset of clinical signs in chronic Cu toxicity is associated with the development of a hemolytic crisis. Affected animals exhibit depression, weakness, rumen stasis, anorexia, hematuria, hemoglobinuria, icterus, incoordination, and ptyalism(89) . Methemoglobinemia, hemoglobinuria, anemia, and decreased blood glutathione concentrations are usually observed during hemolytic crisis(93) as well as a severe decrease in haemoglobin concentration and haematocrit was recorded (99). Animals with these clinical signs and laboratory abnormalities often die within 1–2 days. Although herd morbidity is often ,5%, usually 75% of affected animals die. Furthermore, losses from Cu toxicity may continue for up to 2 months after the dietary problem has been rectified (82).

Copper storage begins in the centrilobular hepatocytes, where most of the copper is sequestered in hepatic lysosomes (100). Lysosomal membranes lose integrity as copper accumulates, and copper lysosomal hydrolases are released, irreversibly injuring the cell . Hepatocellular necrosis and apoptosis occur, the accelerated loss of hepatocytes leads to acute massive copper release causing hemolysis and accumulation of hemoglobin casts in the renal tubules (94). Renal tubular hemoglobinuric casts cause ischemia and direct damage to the epithelium, resulting in tubular necrosis. In acute hepatic toxicity, the metabolic capacity of the liver to store copper is rapidly compromised, and necrosis occurs rapidly with subsequent renal tubular nephrosis due to hemolytic crisis (93). Bile ductular hyperplasia, bridging portal fibrosis, hepatocellular regeneration are (91,101) and damage of the morphometrical structure of testes (102) were recorded in copper toxicity.

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