

Review Article

Copper Poisoning with Emphasis on Its Clinical Manifestations and Treatment of Intoxication

Mehrdad Rafati Rahimzadeh ¹, Mehravar Rafati Rahimzadeh ², Sohrab Kazemi ³ and Ali Akbar Moghadamnia ⁴

¹Department of Nursing, Babol University of Medical Sciences, Babol, Iran

²Department of Medical Physics, Kashan University of Medical Sciences, Kashan, Iran

³Cellular and Molecular Biology Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran

⁴Pharmaceutical Sciences Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran

Correspondence should be addressed to Ali Akbar Moghadamnia; aliamoghadamnia@gmail.com

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Background. Copper is an essential trace element found in the human body in an oxidized (Cu II) and reduced (Cu I) form. It plays a crucial role in the integrity and function of proteins and enzymes. Short-term and long-term exposure to copper can result in harmful effects and lead to clinical manifestations in multiple bodily systems, including the gastrointestinal tract, liver, kidneys, eyes, respiratory, cardiovascular, central nervous, endocrine, and hematopoietic systems. **Objective.** The purpose of this study is the importance of early recognition and diagnosis of copper poisoning immediate and necessary measures and the use of chelators. **Materials and Methods.** In this review article, authors from Pub Med, Scopus, and a toxicologic emergencies reference book from 1996 to 2024 are used. **Result.** An excessive increase in copper level produces reactive oxygen species that can cause lipid peroxidation in cell membranes, direct oxidation of proteins, and the breakdown of DNA and RNA molecules. All of these can generally be reasons for cell death. **Conclusion.** Assessing levels of copper in whole blood, free serum copper, 24-hr urine copper, liver biopsy for copper concentration, and ceruloplasmin play a crucial role in the diagnosis. The blood copper concentration is directly related to the severity of poisoning. Treatment for copper poisoning typically involves removing the source of exposure and administering medications to help remove the excess copper from the body. Supportive care for copper intoxication usually includes managing vomiting, correcting fluids and electrolytes, and stabilizing vital signs. Chelators like D-penicillamine, succimer, trientine, tetrathiomolybdate, and PBT-2 have been utilized in treatment.

1. Introduction

For decades, access to chemicals has been facilitated, and the process of using them has been improved [1, 2]. People may use them either intentionally, negligently, or necessarily, and as a result of repeated consumption, they may be poisoned either deliberately or accidentally [3]. Several of these agents are heavy and essential trace metals. These substances are utilized in natural resources, food, industrial waste, or in food and medical supplements, which can lead to the vulnerability of essential organs in the human body [4, 5].

The oldest metal discovered in the Middle East was copper, dating back to 5100 BC. According to the US Geological

Survey, it is the third most consumed industrial metal in the world after iron and aluminum [6]. In the normal physiological conditions of Cu proenzymes play an essential role, on the other hand, the harmful effects of copper are based on two principles: (1) copper is potentially involved in the generation of reactive oxygen species (ROS), and (2) in the redox reactions, it plays a crucial role as a catalyst in various oxidase enzymes [7]. In adults, to prevent copper deficiency, it is necessary to consume 0.9 mg/day. In addition, to prevent copper poisoning, its amount should be limited to less than 10 mg/day [7].

Acquaintance with the necessity of using copper in the diet, as well as poisoning with it, the necessary knowledge

and awareness about this element is provided. The purpose of this study will be to explain the importance of recognizing signs and symptoms and early diagnosis of copper poisoning. Also, potential complications with copper poisoning will be described. In addition, this study will review therapeutic measures, especially the timely use of chelators.

The importance of the study will be that the knowledge and learnings of the interprofessional and health care team in teaching the patient for prevention, appropriate treatments, the recovery of patients with copper poisoning will be increased, and the death rate will be decreased due to this poisoning.

2. History, Physical and Chemical Properties

The oldest items discovered were copper beads dating back to 9000 BC, along with copper-working tools dating to 5000 BC. Additionally, Native Americans utilized copper objects dating to around 2000 BC. Copper, symbolized by Cu and derived from the Latin word *cuprum*, is named after the island of Cyprus. It and its alloys have been recognized as essential metals from 4000 to 3000 BC. The key reference point is its color, known as reddish-brown. Copper has an atomic number of 29, an atomic mass of 63.546, a melting point of 1,083°C, and a boiling point of 2,595°C. It is a relatively active metal with properties such as high thermal and electrical conductivity, considerable malleability, and the ability to form alloys. Its electrical conductivity and fabricability are closely tied to its purity. Additionally, it is soluble in alkalis and additives. One crucial chemical property of copper is its reaction with oxygen. In humid air, it reacts with water and carbon dioxide to form hydrated copper carbonate ($\text{Cu}_2(\text{OH})_2\text{CO}_3$), resulting in a beautiful green color known as patina [8, 9].

3. Physiology and Biochemistry of Copper in Health and Toxicity

Copper is a vital trace metal present in the bodies of various living beings, including humans. It exists in the human body as oxidized (Cu II) and reduced (Cu I) forms and is crucial for survival. It plays a role in numerous biological processes such as growth and development, antioxidant defense, neuropeptide synthesis, and immune function [10, 11]. It plays a crucial role in the structure and function of proteins and enzymatic systems, including catalase, cytochrome C oxidase, dopamine beta-hydroxylase, and serum ceruloplasmin [12]. Copper is a vital micronutrient for humans, but an excess of it in the body, particularly in cells, can lead to cytotoxicity. The free hydrated form (such as Cu^{2+}) has the potential to be toxic by altering membrane permeability and protein synthesis, as well as various enzymatic activities. Specifically, the generation of hydroxyl radicals ($\text{HO}\bullet$) and/or other ROS have been attributed to the reaction of copper with hydrogen peroxide (H_2O_2), resulting in organized lipid peroxidation in membranes, direct oxidation of proteins, and the degradation of DNA and RNA molecules [10, 11, 13].

4. Metabolism

Studies indicated that copper intake is affected by the amount of copper in one's diet and the balance of copper in their body. Additionally, copper intake depends on factors such as age, gender, type of food, and the quantity of dietary copper consumed [10, 14]. In adults, the typical dietary intake of copper is estimated to be around 0.6–1.6 mg/day, sourced from a variety of foods [15]. Most of the copper absorption occurs through the mucous membrane in the stomach and duodenum cells, which are the primary sites for copper absorption in the upper GI tract. The metal ion adsorption efficiency is high, with adults showing apparent adsorption values between 55% and 75%, which remain relatively constant with age. It is worth noting that copper in the diet contributes only a small portion to the overall reabsorption compared to other bodily fluids, such as saliva, gastric juice, duodenum, bile, and pancreas [10, 11]. After being absorbed into intestinal mucosal cells and passing through the basolateral membrane, copper is transported to the interstitial fluid and blood by various mechanisms. In the interstitial fluids and plasma, copper binds to two proteins (albumin and transcuprein) in portal blood and general circulation, with most of this bound copper quickly heading to the liver. Human plasma is rich in albumin, which has a high affinity for copper, while the remaining copper binds to ceruloplasmin, transcuprein, and low molecular weight components. Therefore, copper is not directly bound or combined with ceruloplasmin ions, but is added by the liver during ceruloplasmin synthesis [15]. Most of the exchangeable copper pool in blood plasma is completed by albumin and transcuprein, as mentioned. Copper on ceruloplasmin is accessible for uptake in other tissues. Under normal conditions, ceruloplasmin is likely to be the main source of copper for other tissues, and there is no need to uptake copper by albumin in the liver and kidneys. Existing research is based on this: Most non-liver tissues, especially the heart and placenta, prefer to uptake copper from the ceruloplasmin–copper combination due to the presence of specific receptors in the plasma membrane. Importantly, the ceruloplasmin–copper composition is not the only form of copper in most nonhepatic tissues. Still, existing studies have shown that copper can be up taken from ceruloplasmin, albumin, transcuprein, and copper-dihistidine [11, 16].

In relation to copper distribution within cells, it should be noted that Cu(I) is highly detrimental due to its free ions and reactive nature, causing damage to cell membranes, nucleic acids, and proteins. Copper is transported to specific molecules in the form of complexes with small cytosolic proteins, such as copper chaperone proteins. These chaperones are intracellular proteins that shield copper from entering the cell through the cytoplasm to intracellular targets. Upon passing through the enterocytes, most of the copper is transferred to the trans-Golgi network (TGN). In enterocytes, ATP7A is responsible, while in the liver, it is ATP7B. The chaperone protein CCS delivers copper to copper/zinc superoxide dismutase (SOD) in the cytoplasm, protecting cells from superoxide radicals. Additionally, the COX 17 gene delivers copper to the mitochondria, where cytochrome C oxidase, the terminal enzyme necessary for respiration, is located [17–19]. Another important point is the role of glutathione (GSH) as an antioxidant; it acts as a general

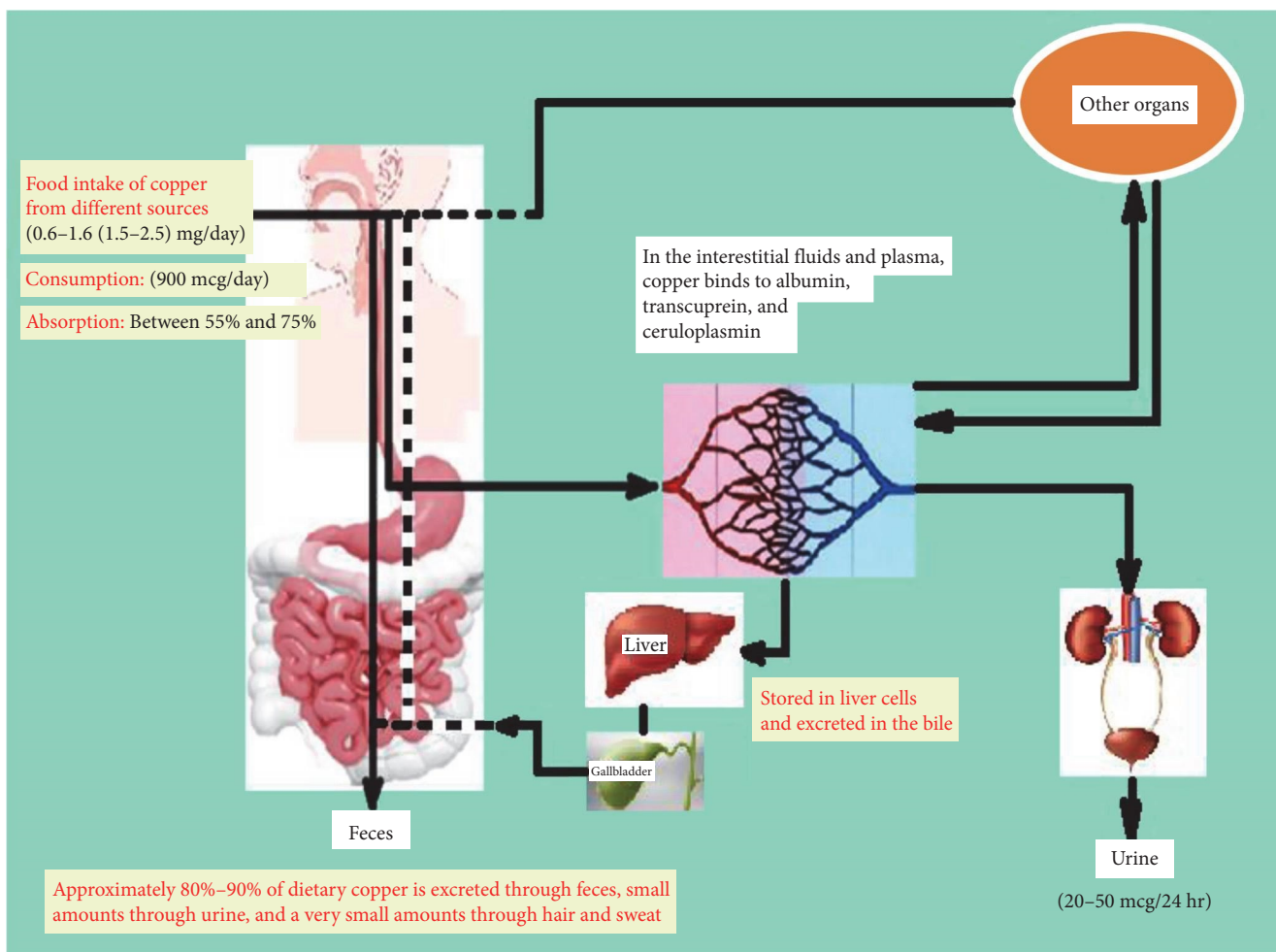


FIGURE 1: Copper metabolism in human.

chaperone for copper ions, facilitating the delivery of copper to the copper transporter 1 (CTR1) in the plasma membrane. In vitro studies have shown that reduced glutathione is bound with Cu(I). The copper-glutathione complex can effectively deliver stable Cu(I) to apo (nonmetal)-cuproproteins. These studies demonstrate that Cu-GSH can transport copper(I) to the apo-CuZnSOD, apo-hemocyanin, and apo-ceruloplasmin sites, as well as charge metallothionein with Cu(I). Metallothionein plays a role in zinc and copper homeostasis, defense against oxidative stress, and buffering against toxic heavy metals. While glutathione may not be necessary for distributing copper in the cell, it is required to restore the ability of copper-binding proteins (with the thiol group) to bind their copper [20].

Based on current knowledge, copper is stored in liver cells as ceruloplasmin, released into the bloodstream, and excreted in the bile. The primary method of copper excretion is through the bile, which plays a crucial role in regulating copper levels in the liver [14, 21]. In copper homeostasis, the liver plays the primary role in regulation, while the kidneys also have a secondary role in copper excretion [14]. It is important to note that, excluding the secretions of the gastrointestinal tract (salivary glands, pancreas, and epithelium in the stomach and intestines), most copper returns to the

liver for excretion. Transcuprein and albumin act as plasma carriers that specifically target the liver and ceruloplasmin. Ceruloplasmin primarily enters liver cells through endothelial cells after desialylation, a process that modulates the structure and function of glycans, glycoproteins, or glycolipids [11]. Ceruloplasmin, albumin, and amino acids facilitate the transport of copper to tissues outside the liver or its excretion into the bile. The liver exerts hemostatic control over extrahepatic copper by regulating intrahepatic enzymes, binding proteins to exchanged or unexchanged copper, and ultimately controlling copper release [16, 20].

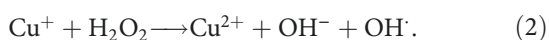
At least half of the copper that reaches the small intestine is excreted in the bile and lost through feces. Therefore, the loss of copper in feces is closely related to diet, and changing the diet in relation to copper sources can greatly impact the balance of copper. However, changes in dietary copper have little to no effect on urinary copper. Therefore, regulating the absorption and endogenous excretion of copper in the body is crucial for controlling and preventing copper deficiency or poisoning [20, 21] (Figure 1).

4.1. Mechanisms of Copper Poisoning. Organisms have mechanisms for regulating the import, separation, and

export of compounds to protect against metal-induced toxicity. These mechanisms are regulated by metal-bound proteins at the transcriptional, translational, and enzymatic levels. The state of adsorption, transfer, distribution, and excretion of copper, as well as copper homeostasis in general, were explained. Disruption in copper homeostasis is accompanied by organ damage and several diseases.

Cells regulate the accumulation of transport metal ions, such as copper, and maintain the amount needed for biological function. Among the factors required for metal ion homeostasis are metallochaperones, which guide and protect transient metal ions inside the cell and deliver them confidently to suitable protein receptors. These chaperone copper and its homologues in humans deliver copper to the antioxidant enzyme copper-zinc superoxide dismutase (SOD1) and its colony in the human body. The interaction between copper chaperone for superoxide dismutase (CCS) and SOD1 is important in body tissue. The consequences of these findings are profound, and the dysregulated concentration of transition metal ions such as copper in cells will be associated with disease in humans [22, 23].

Another important point to note is the tendency of free Cu ions to interfere with the release of free radicals and cause oxidative damage, leading to copper poisoning. Copper ions can undergo reductive-oxidation cyclic reactions, resulting in the formation of free radicals and oxidative damage. This is due to the formation of ROS. Numerous studies on copper poisoning have indicated that the affinity of copper ions for the forming of ROS can alter the structure and function of essential biomolecules [24]. The presence of superoxide-producing agents and the decrease or lack of antioxidants like ascorbic acid, selenium, or glutathione can lead to the reduction of Cu^{2+} to Cu^+ (Cu^{2+} only needs one electron to be reduced), which has the potential to catalyze the conversion of hydrogen peroxide (H_2O_2) into hydroxyl radicals (OH^\bullet) through the Haber–Weiss reaction [24, 25]:



In the biological system, the hydroxyl radical is likely to form, as it is the strongest oxidizing radical. It can react with any biological molecule. When hydroxyl radicals form with copper metal, they remove a hydrogen from an unsaturated fatty acid, leading to the formation of fat radicals. This action initiates a reaction cascade that ultimately destroys the lipid bilayers. Additionally, hydroxyl radicals can abstract a hydrogen from the amino-bearing carbon, generating a carbon-centered protein radical which, through a series of reactions, leads to the hydrolysis of the amino group [26, 27]. Copper is well known for its effectiveness in producing ROS, which in turn induce various types of DNA damage. This includes causing single-strand breaks (SSBs) in the DNA, which are usually quickly repaired. However, when multiple SSBs occur, they can be transformed into double-strand breaks (DSBs). DSBs are closely associated with cell death if left unrepaired. Unrepaired DNA strand breaks can lead to

widespread cell death [27]. Copper, capable of producing ROS, also oxidizes bases [25].

Another important point in copper poisoning is that copper induces low-density lipoprotein (LDL) oxidation. Additionally, copper ions involve ceruloplasmin, which is the source of free copper in LDL oxidation. This action can create an atherogenic form by modifying LDL. It is possible that Cu^{2+} binds to the histidine remaining apolipoprotein B100 on the LDL molecule, and this process reduces the Cu^+ form. Cu^+ reduces lipid hydroperoxides to alkoxy radicals. In fact, lipid peroxidation is an implication of oxidative cell damage. Protein oxidation also initiates the introduction of carbonyl groups in proteins, making the oxidized proteins nonefficient. Lipid peroxidation and protein oxidation cause membrane damage, dysfunction of cells, and destruction of DNA. All of these actions increase the transfer of macrophages into the foam cells, leading to vasoconstriction and a prothrombotic process [25, 28].

In oxidative conditions, nitric oxide and superoxide anion can be produced, which together form significant amounts of the oxidatively active molecule known as peroxynitrite anion (ONOO^-) [29]:



The peroxynitrite anion is a potent cytotoxic oxidant with the capacity to oxidize lipids, damage proteins, and degrade DNA. Additionally, it interferes with the transport of the protein ceruloplasmin and releases copper ions, leading to the formation of a copper–lipoprotein complex, which triggers lipid peroxidation [29]. It is directly involved in the oxidation of LDL. Furthermore, endothelium-derived nitric oxide is suggested to prevent platelet adhesion and vasospasm in vessels [25]. Research has indicated that high-density lipoprotein (HDL) is more susceptible to copper-induced peroxidation than LDL at the same cholesterol level. HDL contains a higher amount of copper attached to lipoprotein lipids at elevated copper levels, enhancing its ability to oxidize [25, 30].

In copper poisoning, the production of highly reactive hydroxyl radicals through the Fenton and Haber–Weiss reactions damages lipids, proteins, and DNA, significantly affecting the cell's life, tasks, and functioning [23]. Various studies indicate that copper poisoning can occur through a variety of mechanisms and pathways, including dysregulation of lipid metabolism, impaired antimicrobial defense, disorganization of neural activity, resistance of tumor cells to chemotherapy drugs, and other disruptions of fundamental cellular processes, ultimately leading to cell dysfunction and death [31] (Figure 2).

4.2. Clinical Manifestation. Symptoms of copper poisoning related to the gastrointestinal tract include nausea, vomiting, and abdominal pain at the onset of poisoning, which is the most common and first symptom. In severe cases, this may be followed by gastrointestinal bleeding, ulceration, or perforation [32, 33]. Copper is then carried to the liver and other tissues by protein carriers, ceruloplasmin, and albumin,

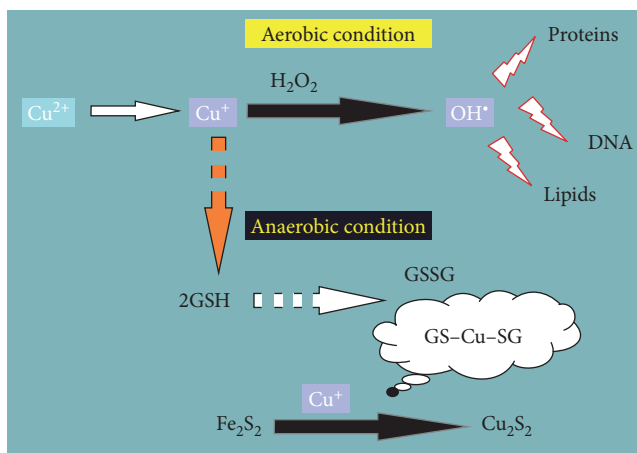


FIGURE 2: Mechanism of copper poisoning in aerobic and anaerobic conditions.

where it can lead to liver damage, methemoglobinemia, and rhabdomyolysis [32]. The copper release from the liver leads to a significant rise in blood copper concentration and an increase in specific liver enzymes in the plasma. This is linked to extensive hepatic degeneration and focal necrosis, cell inflammation, bile plugs, and positive periodic Acid-Schiff (PAS) Kupffer cells in the liver [34].

Hematologic changes have been reported: The levels of RBC and WBC, as well as hemoglobin content, are significantly decreased in individuals with copper poisoning [35]. The effects of intravenous hemolysis due to copper contact led to hemoglobinuria, causing issues such as tubular necrosis, lack of mitochondrial enzyme activity in the tubules, and acute renal failure. Acute copper sulfate poisoning may result in irreversible chronic tubulointerstitial nephritis [34, 36]. The presence of a Kayser–Fleischer (KF) corneal ring and sunflower cataract (SC) are indicative of copper deposition in the Descemet layer of the cornea. The SC is characterized by a thin, central opacity beneath the anterior capsule, and surrounding the surface of the anterior pole of the lens [37, 38].

The widespread presence of copper in industrial appliances, households, and the atmosphere has adverse effects on the respiratory system and clinical manifestations. Cupric oxide (CuO) nanoparticles have a strong capacity to induce oxidative stress and endanger the respiratory system, exacerbating or causing respiratory diseases [39]. Increased lung inflammation, cellular damage, and degeneration of the nasal epithelium have been observed [40]. The induction of oxidative stress in the system will be accompanied by acute respiratory distress syndrome, cystic fibrosis, idiopathic respiratory fibrosis, and will cause impaired respiratory function and airway obstruction [41]. Pulmonary function parameters such as expiratory reserve volume (ERV), forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), FEV1/FVC, peak expiratory flow rate (PEFR), mid expiratory flow 50% (MEF50%), mid inspiratory flow 50% (MIF50%), and forced expiratory flow 25%–75% (FEF 25–75) were significantly decreased in cases of copper poisoning. Specifically, FEV1 is the first measurable amount to be assessed at the onset of bronchitis and obstructive pulmonary disease. The obstructive pattern of the lungs is due to inflammatory reactions,

respiratory irritation, and narrowing of the airways. With chronic exposure to copper, chronic inflammation of the parenchyma and pulmonary system occurs [42]. Copper ions can catalyze oxidative changes and are a major component of lysyl oxidase involved in collagen biosynthesis, a key part of the arterial wall's extracellular matrix [43]. Several studies indicate that high copper concentrations are linked to the onset of cardiovascular disease, directly impacting vascular endothelium and indirectly affecting lipoprotein metabolism [44]. One such disease is atherosclerosis, marked by ongoing artery inflammation, LDL oxidation, and the generation of free radicals [45]. In cases of severe copper poisoning, hypotension, tachycardia, and cardiovascular collapse occur after a few hours, leading to other complications or early death [12]. Following gastrointestinal absorption of copper, intravascular hemolysis may occur after 12–24 hr. Significant methemoglobinemia occurs early in the clinical course following hemolysis. Studies have also shown an increase in the number of erythrocytes and hematocrit, and a decrease in hemoglobin levels. This decrease could be attributed to the interaction of copper with the enzymes responsible for hemoglobin production. Additionally, coagulopathy occurs due to the direct impact of free copper ions on the coagulation cascade [12, 35, 46].

Reduced central nervous system activity, ranging from lethargy to coma or seizures, may be linked to the involvement of other organs. Copper imbalances have significant effects on the central nervous system [12]. Wilson's disease is characterized by tremors (such as classic wing-beating or flapping tremors), dystonia, parkinsonism, ataxia, dysphagia, dysarthria, and drooling. An increase in free copper concentration in the serum leads to decreased cognitive function in Alzheimer's disease. Hypomimia, shuffling gait, impaired movement of the fingers, and foot tapping are also common features of Parkinsonism, which is associated with copper poisoning. The psychiatric consequences of copper imbalance are extensive, ranging from anxiety to violence, obsessive-compulsive disorder, bipolar disorder, phobias, mild-to-moderate depression, and ultimately suicide, Tourette's syndrome (involving repetitive movements or unwanted sounds, known as tics), and schizophrenia [12, 47, 48]. Various endocrinopathies associated with copper poisoning include increased prolactin and insulin release, as well as abnormal menstruation. Hyperprolactinemia may be due to elevated prolactin levels in glandular tissue, resulting from increased copper accumulation in the mammary gland. Symptoms of hypoglycemia include sweating, paleness, hand tremors, and palpitations. Menstrual abnormalities typically begin as oligomenorrhea and can progress to amenorrhea. Premenstrual syndrome (PMS) symptoms are linked to estrogen and copper levels, both of which increase before menstruation. Infertility is more common in women with high copper levels. In men, symptoms of copper poisoning include an enlarged prostate, prostate infections, and to some extent, prostate cancer. Other notable effects include impotence, depression, anxiety, and even violence [12, 49, 50]. There is no evidence that copper has carcinogenic properties. Recent studies have shown that copper does not cause mutagenicity [51].

4.3. Diagnostic Evaluation. Real-time copper poisoning testing is nearly impractical, so treatment decisions rely on

clinical findings and existing criteria. However, various copper levels—such as whole-blood copper, free serum copper, 24-hr urinary copper, liver biopsy copper concentration, and ceruloplasmin—are assessed to diagnose copper poisoning-related issues. Whole-blood copper typically ranges from 70 to 140 $\mu\text{g}/\text{dl}$, while free serum copper is around 4–7 $\mu\text{g}/\text{dl}$. Notably, due to rapid copper movement from serum to red blood cells, it is preferable to focus on whole-blood copper concentration over serum copper concentration. Moreover, there exists a significant correlation between whole-blood copper concentration and poisoning severity. In cases of copper poisoning, urinary copper excretion typically ranges from 5 to 25 μg in 24 hr, exceeding normal levels [52]. The primary step in determining liver copper biopsy involves two stages of liver biopsy and obtaining a complete core of liver biopsy specimen to assess copper levels. Biopsy of the entire liver core reduces specimen variability caused by varying copper concentrations. The normal hepatic copper concentration ranges from 15 to 55 $\mu\text{g}/\text{g}$ of dry liver [53]. Ceruloplasmin serves as the primary carrier of copper in the blood, transporting 65%–90% of all copper in the plasma of a healthy individual. Its concentration in humans typically ranges from about 20–35 mg/dl. In cases of acute copper poisoning, serum ceruloplasmin concentrations may rise, but this is likely due to increased hepatic synthesis, and this elevated ceruloplasmin cannot be used to determine the patient's prognosis [52, 54].

4.4. Treatment

4.4.1. Supportive Care. The key principle in the effective management of patients with copper poisoning, particularly in acute cases, is to address vomiting, balance fluids and electrolytes, and stabilize vital signs before administering chelation agents. Ingesting copper compounds can lead to nausea, vomiting, and aspiration. To prevent further exposure of the gastrointestinal tract to corrosive agents, the patient needs antiemetic therapy. The benefits of consuming activated charcoal have not been proven, but it is not expected to be harmful. The standard dosage is 25–100 g for adults and 25–50 g for children aged 1–12 years [12, 52].

4.4.2. Methemoglobinemia. It is important to monitor methemoglobin levels in patients with methemoglobinemia. If the level exceeds 20%–30% and the patient shows symptoms, methylene blue must be administered. If the methemoglobin level is below this range, oxygen therapy in combination with methylene blue is necessary. Methylene blue works by enhancing the activity of the enzyme methemoglobin reductase, thereby improving the conversion of methemoglobin to hemoglobin. The initial intravenous dose is 1–2 mg/kg of body weight over 5 min. If cyanosis persists after 1 hr, the dose should be repeated. For methemoglobin levels surpassing 70%, the half-life of methylene blue is reduced from 15–20 hr to 40–90 min, so improvement should be observed within 1 hr after administration [55]. If severe hemolysis occurs, methylene blue will not be effective; however, if methylene blue is used in doses greater than 5–7 mg/kg, it can directly cause the oxidation of hemoglobin, leading to a higher level of methemoglobin [54, 56]. In these conditions, an exchange

transfusion or hyperbaric oxygen can be used. Ascorbic acid is used as an alternative treatment in methemoglobinemia. It is a strong reducing agent, participates in many oxidation–reduction reactions and reduces the amount of methemoglobinemia. On the other hand, ascorbic acid does not play a role in acquired methemoglobinemia [57]. N-acetylcysteine is considered effective in some studies, but its function has only been performed in vitro, not in vivo [56, 58].

4.4.3. Rhabdomyolysis. Copper poisoning leads to rhabdomyolysis, with copper deposition in peripheral muscle tissue causing tissue damage. D-penicillamine is a chelator used in treating acute copper poisoning, but its use has not been proven to cause acute rhabdomyolysis. If patients struggle to adapt to the copper overload, copper is excreted in the urine, leading to increased copper excretion during chelation therapy. Zinc can prevent intestinal absorption of copper through competition or by producing metallothionein in epithelial cells. Zinc does not cause nephrotoxicity or acute rhabdomyolysis, making it a viable method. Additionally, daily fluid replacement, fluid monitoring, osmotic diuretics, and urine alkalinization can be helpful measures for fluid control [55, 59].

4.4.4. Chelation Therapy. Chelating agents are initiated when hepatic or hematologic complications arise in patients with copper poisoning or when severe clinical manifestations are present. Due to the limited efficacy of chelator therapy in acute copper poisoning and the inconsistent results, it is challenging to assess the impact of chelator therapy, and even when administered promptly and appropriately, organ vulnerability and even death have been reported [52].

(1) *British Anti-Lewisite (BAL)*. Most patients with copper poisoning are typically treated with BAL, particularly for those experiencing vomiting or gastrointestinal tract damage, as BAL is administered intramuscularly. The recommended dosage is 3–5 mg/kg of body weight deep intramuscularly every 4 hr for 2 days, followed by the same dose every 4–6 hr for another 2 days, then every 4–12 hr for more than 7 days. Common side effects include urticaria and persistent hyperpyrexia (Table 1) [12, 52].

(2) *Calcium Disodium Ethylenediaminetetraacetate (CaNa₂EDTA)*. Copper ions cause oxidative harm, and EDTA mitigates these effects, although it cannot eliminate a large portion of copper. Conversely, it is swiftly deactivated by dopamine beta-hydroxylase; however, this enzyme can be reactivated by the addition of exogenous copper. Yet, the mechanism of inhibiting neural norepinephrine formation during treatment in acute intoxication conditions remains unclear. The therapeutic dosage of this medication is 75 mg/day, administered deeply into the muscle or slowly through intravenous infusion in three to six divided doses over a period of more than 5 days. It may be administered for an additional period with a minimum dose of 2 days, with each period not exceeding 500 mg/kg. Side effects of this medication include renal tubular necrosis (Table 1) [52, 55].

(3) *D-Penicillamine (Cuprimine)*. D-penicillamine can also be used to treat copper poisoning and is involved in preventing the induction of hemolysis by copper in patients with Wilson's disease. Additionally, it is used to treat chronic

TABLE 1: Main copper chelating agents.

S. no.	Compound name and abbreviation	Chemical formula	Structural formula
1	British anti-lewisite (BAL)	$C_3H_8OS_2$	
2	Calcium disodium ethylenediaminetetraacetate (CaNa2EDTA)	$C_{10}H_{12}CaN_2Na_2O_8$	
3	D-penicillamine (DPA): (S)-2-amino-3-mercapto-3-methylbutanoic acid	$C_5H_{11}NO_2S$	
4	2,3-Dimercaptosuccinic acid (DMSA) [†]	$C_4H_6O_4S_2$	
5	Unithiol (DMPS) [‡]	$C_3H_8O_3S_3$	
6	Triethylenetetramine dihydrochloride (TETA)	$C_6H_{18}N_4$	
7	Tetrathiomolybdate (TM)	MoS_4	
8	5,7-Dichloro-2 [(dimethylamino) methyl] quinolin-8-ol (PBT2)	$C_{12}H_{12}Cl_2N_2O$	
9	Clioquinol (CQ)	$C_9H_5ClI NO$	

[†]Recently, it is less used for copper poisoning. [‡]Currently, this agent is not used in copper poisoning due to adverse effects.

exogenous copper poisoning. Its protective mechanism primarily involves chelating nonbound copper to prevent their participation in reduction–oxidation reactions. In a healthy kidney, the D-penicillamine–copper complex is rapidly excreted. The patient is typically given 1–1.5 g of D-penicillamine orally, divided into two to four doses. Due to severe side effects of D-penicillamine, such as pancytopenia, renal toxicity, polyneuropathy, ocular neuritis, and polymyositis, especially worsening of the nervous system, toxicologists have recommended low doses of D-penicillamine and high doses of zinc. The recommended dose is as follows: a low dose of D-penicillamine is 8–10 mg/kg of body weight/day, along with a high dose of zinc sulfate (100–150 mg in children under 6 years, 150–200 mg in children aged 6–8 years, 200–300 mg in 9–10-year old, and 300 mg for those over 10 years; three times a day) at the beginning of treatment. This combination therapy is more effective, safer, and more cost-effective, making it suitable for a wide range of copper poisoning cases. Furthermore, the use of D-penicillamine in patients allergic to penicillin is prohibited. Additionally, the application of D-penicillamine during pregnancy is prohibited due to its potential to cause congenital malformations in the fetus (Table 1) [52, 58, 60].

(4) *Succimer (DMSA) and Unithiol (DMPS)*. Most studies have shown that Succimer (DMSA) is not effective as a copper chelator. In certain documented research, it may be used for mild-to-moderate copper poisoning in place of D-penicillamine. This is because DMSA has a dithiol structure that can counteract the harmful effects of Cu(I), resulting in fewer clinical symptoms compared to D-penicillamine. Additionally, DMSA has fewer side effects, making it a preferred option over D-penicillamine for its short-term and long-term therapeutic effects (Table 1) [52, 58, 59]. Unithiol (DMPS) has been proposed as a chelator that effectively eliminates copper from the urine of normal (noncopper poisoned) individuals. However, DMPS forms more intramolecular disulfide bridges than D-penicillamine, which reduces its effectiveness and may account for the exacerbation of copper-induced hemolysis *in vitro*. Due to increased hemolysis and undesirable side effects, it is not used in copper poisoning. New chelators have now replaced DMSA and DMPS in the treatment of copper poisoning (Table 1) [61, 62].

(5) *Trientine*. Triethylenetetramine (TETA), also known as trientine, is in patients who have severe intolerance to D-penicillin, this agent is considered an oral chelating agent and has less adverse effects. Evidence based on reduction of body copper stores of “decoppered” and improvement of clinical symptoms was reported by Trientine [63]. TETA causes copper to be excreted in the urine and studies have shown it to be safer. The initial dose of TETA is between 900 and 2,700 mg/day, with a maintenance dose of 900–1,500 mg/day (20 mg/kg/day), which should be taken in divided doses. It is recommended to take it 1 hr before or a few hours after a meal. TETA has few side effects, with reversible sideroblastic anemia and, in some cases, pancytopenia being seen because of over-treatment. Other reported side effects include lupus-like syndrome, bleeding gastritis, loss of taste, and rash (Table 1) [64, 65].

(6) *Tetrathiomolybdate (TM)*. Ammonium tetrathiomolybdate is a specific copper chelator that reduces the body's ability to absorb copper. It has been approved by the FDA after successful clinical trials. Available data indicate its effectiveness in treating diseases characterized by excessive copper, particularly in addressing the neurological disorder Wilson's disease. Research suggests that neurodegenerative diseases treated with this compound show significant reduction. Consequently, it holds promise for efficacy with limited toxicity. However, its use is restricted due to the instability of the ammonium formulation and the requirement for consumption six times a day [66, 67]. In most studies, the prescribed dose of tetrathiomolybdate is 120 mg/day, administered as 20 mg three times daily with meals and 20 mg three times daily between meals for 8 weeks [68]. Side effects may include mild bone marrow suppression leading to anemia, leukopenia, and occasionally thrombocytopenia, as well as slightly elevated aminotransferase enzymes (Table 1) [69].

(7) *Nitrilotriacetic Acid (NTA)*. Nitrilotriacetic acid (NTA) is widely used in metal ion chelation, particularly for Cu²⁺ chelates. Its functionality is akin to that of EDTA but with the added benefit of easy biodegradability. It is typically employed as Na₃NTA or FeNTA [64]. The rationale for its use is as follows: Copper finds its way into water ecosystems through various channels and has the capacity to accumulate over time, leading to water contamination and resulting in numerous disorders and diseases in aquatic organisms. Nitrilotriacetic acid, being an aminopolycarboxylic acid, can chelate metals with its carboxyl functional group. It can form bonds with toxic metals like Cu(II) ions through mixed or electrostatic reactions. Adsorption technology has demonstrated its effective surface performance [70]. Furthermore, these metal complexes may contribute to metal uptake by plants. Research indicates that the presence of organic ligands can mitigate the toxicity of copper. Naturally, the toxicity of copper aligns with the activity of free copper, and it is contingent on the nature of organic ligands and the flexibility of copper–organic complexes, such as NTA [71].

(8) *8-Hydroxyquinolines and Cloiquinol*. Other chelators classified as nonselective chelators against copper poisoning are 8-hydroxyquinolines. One of the halogenated derivatives of 8-hydroxyquinoline is cloiquinol (CQ), and studies suggest that the chelating action of cloiquinol can also include zinc, iron, and copper [72]. However, it was discontinued in the 1970s due to subacute myelo-optic neuropathy (SMON) [64, 73, 74]. The attenuated metal–protein compound is known as idochlorhydroxyquin in the preclinical stage, also developed as PBT-1 or cloiquinol, and further as PBT-2, which has clinical application. PBT-2 is the second generation of 8-hydroxyquinoline, which does not cause neuropathic problems for consumers [74, 75]. PBT-2 has pharmacological properties equivalent or greater than cloiquinol, with higher solubility, the ability to cross the blood–brain barrier, and demonstrated effectiveness in preclinical stage *in vivo* studies (Table 1) [75, 76].

5. Acute Respiratory Distress Syndrome (ARDS) and the Role of Extracorporeal Membrane Oxygenation (ECMO) Therapy

The Extracorporeal Life Support Organization (ELSO) recommends venovenous extracorporeal membrane oxygenation (ECMO) for patients with acute respiratory distress syndrome (ARDS). The organization's criteria for these patients include using a mechanical ventilator and a PaO₂/FIO₂ ratio <150 on FIO₂ >90%. To achieve ideal oxygenation with venovenous ECMO, the pump blood flow must be ≥60% of the cardiac output (CO), PaCO₂ should be maintained at 30–40 mmHg, and the device should deliver enough oxygen to maintain arterial oxygen saturation (SaO₂) above 88% [77, 78].

6. Extracorporeal Elimination

There is insufficient information and research on using various extracorporeal methods for eliminating copper ions. Regarding exchange transfusion, the available information is limited and it is impossible to accurately judge this method's effectiveness in preventing acute copper poisoning [52]. Additionally, while dialysis or hemoperfusion may increase copper excretion, it has not been proven because copper is bound to serum and tissue proteins. However, copper chelated by diuresis and dialysis is excreted from the serum. It can be argued that hemodialysis is only indicated in cases of acute persistent renal failure, and it is important to note that copper excretion through the kidneys will be minimal because the main route of excretion is through the bile [79, 80]. Peritoneal dialysis is not adequate for maintaining a relatively long-term condition until renal function has returned to health and would be an option if hemodialysis is not available [81]. Intravascular copper ions are tightly bound to serum proteins such as ceruloplasmin, albumin, and gamma-globulin, preventing them from passing through the dialysis membrane. Therefore, clinicians recommend plasmapheresis over hemodialysis. If plasmapheresis is not available, hemodialysis may be used [82]. There are also reports of using direct hemoperfusion and hemodiafiltration to remove chelated copper and nephrotoxic substances, preventing the progression to acute renal failure [79]. Generally, advanced treatment for patients with renal failure may involve hemodialysis, while patients with hepatic failure may require liver transplantation [52].

7. Conclusions in the Field of Copper Poisoning

Copper poisoning is uncommon and rare, but its effects are severe and tragic and cause the death of patients. Therefore, it is very important to limit the exposed people to food and drink contaminated with copper, and copper utensils, to recognize the signs and symptoms of poisoning, to be quick in the early diagnosis, and to understand the severity of the disease stages. Fortunately, extensive research has been conducted on copper metabolism diseases, particularly Wilson disease, which resembles acute copper poisoning during exacerbated periods and provides valuable insight into treating

patients with acute copper salt poisoning. The primary effects involve oxidative stress on red blood cells and liver cells. It is a part of symptomatic treatment, however, chelation therapy is very important. D-penicillamine is the primary traditional chelator for treating copper poisoning, but succimer is often preferred by clinicians due to its fewer side effects. Newer chelators like trientine, tetrathiomolybdate, and PBT2 have been introduced for treating copper poisoning. Limited information is available regarding extracorporeal elimination and is unlikely to be helpful.

The importance of educating the patient by an interprofessional team for prevention, as well as the knowledge of the health care team about copper poisoning, the speed of diagnosis, the timely use of therapeutic measures, especially the use of chelators, plays a vital role and it reduces mortality from copper poisoning.

Data Availability

The authors confirm that the data and materials supporting the findings of this study are available in the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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