IAMJ

INTERNATIONAL AYURVEDIC MEDICAL JOURNAL

Research Article ISSN: 2320-5091 Impact Factor: 6.719

AN EFFECT OF COPPER TOXICITY IN RELEVANCE TO PUBLIC HEALTH

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https://doi.org/10.46607/iamj0110102022

(Published Online: October 2022)

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Article Received: 20/08/2022 - **Peer Reviewed:** 09/09/2022 - **Accepted for Publication:** 26/09/2022

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ABSTRACT

Copper is an essential trace mineral that is vitally important for physical and mental health. Generally, copper is not poisonous in its metallic state but some of its salts are powerful inhibitors of endogenous enzymes present in our body. The poisonous compound of copper is $CuSO_4$, copper carbonate, and copper sub-acetate. The incidence of copper toxicity is very common nowadays. Inhalation, consumption of food and water, and dermal contact with air, water, and soil that contains copper were some exposures medium for copper toxicity. After consumption, copper first starts depositing in the liver thereby disabling the liver to detoxify elevated copper levels in the body thus adversely affecting the nervous system, reproductive system, adrenal function, connective tissue, learning ability in newborn babies, etc. If a large amount is taken at once, it will cause severe vomiting, and abdominal pain, and purging afterward produces headache, and in fatal cases, convulsions or paralysis may occur, which result in death. Chronic poisoning may develop through ingesting small amounts of copper daily, as in cooked or pickled articles, for a length of time. This review article provides an overview of copper toxicity: acute and chronic poisoning, general symptoms, mode of administration, medico-legal and forensic aspects, possible detection methods, and treatment, etc

Keywords: Copper poisoning, Heavy metal toxicity, Chronic poisoning, Copper sulphate, Medicolegal aspects.

INTRODUCTION

Copper *(tamba)* as a metal is not poisonous. In the human body, the copper content is about 100-150 mg which is present as an integral and functional moiety of proteins and enzyme systems including catalase, cytochrome C oxidase, dopamine β-hydroxylase, and serum ceruloplasmin. However, as the body cannot synthesize copper, the human diet must supply regular amounts for absorption[1]. Copper is a reddish-brown nonferrous mineral that has been used for thousands of years by many cultures. The name for the metal comes from *Kyprios*, the Ancient Greek name for Cyprus, an island that had highly productive copper mines in the ancient world. Its atomic number is 29, placing it among the transition metals. This metal is a good conductor of both electricity and heat, and that's why copper can be found in numerous electronic appliances. It is also used to make cooking pots. This metal is also relatively corrosion resistant. For this reason, it's often mixed with other metals to form alloys such as bronze and brass. The properties of this metal closely resembled silver and gold. Modern life has a number of copper applications, ranging from coins to pigments, and demand for this metal remains high, especially in industrialized nations. Consumers interact with it in various forms in their daily today life. This can lead to serious environmental problems, especially when mining companies engage in unsound practices. The chemicals used to extract the metal can be toxic, as can the discarded elements and run off associated with its purification. Many countries take to attempt to regulate their copper industries and the problems associated with it [2]

TOXIC SALTS OF COPPER[3]

S.N.	Chemical Name	Common Name	Features
01	Copper sulphate	Blue vitriol, Nila tutia	Crystalline blue powder
02	Copper subacetate	Verdigris, Zangal	Crystalline green powder
03	Copper acetoarsenite	Paris Green	Emerald green powder
04	Copper arsenite	Scheele's Green	Greenish powder
05	Copper carbonate	Mountain Green	Crystalline green powder

USES[4]

- Manufacturing electrical goods, vessels, alloys, and coins, it is used as a jacket in the bullet.
- Manufacturing pigment, insect repellants, insecticides, and pesticides.
- Largely used in the art industry.
- $CuSO_4$ has also been used as cattle poison and for inducing abortion.
- To impart rich green color to preserved and tinned peas and other green vegetables.

SOURCES OF COPPER[5]

A. Environmental Copper exposure

- **Copper Water Pipes:** Copper plumbing was hailed as a great advance in the 1940s and today the majority of homes in India have copper plumbing. Especially in areas with acidic water, copper can be leached from pipes, leaving in severe cases, a greenish ring on bathroom fixtures. Water coolers and icemakers in refrigerators also use copper tubing. Water that sits in these units can contain dangerously high levels of copper.
- **Copper Cookware:** Copper tea kettles and other copper cookware can be a source of copper toxicity if used frequently over a period of time.
- **Drinking Water Contaminated with Copper:** Some areas of India have high amounts of naturally occurring copper in their water supply. Also, copper sulfate is added to some municipal drinking water supplies to kill yeast and fungi.
- **Birth Control Pills and Copper Intrauterine Devices:** One of the side effects of the pill is that it tends to raise copper levels in the body. This is due to the close association between the hormone estrogen and copper levels. Several hundred milligrams of copper a year can easily

be absorbed from a copper IUD. Many women still use the Copper-T intrauterine birth control device, although it has been taken off the market. The only intrauterine birth control device sold today, however, is a copper-T. These devices can be very harmful to women prone to high copper levels.

- **Vitamin and Mineral Supplements:** Copper is frequently added to vitamin supplements, particularly prenatal vitamins. Although this is a benefit for some people, it can be harmful to many other women.
- **Fungicides for Swimming Pools and Foods:** Copper sulfate is added to swimming pools and may be sprayed on fruits and vegetables to retard the growth of algae and fungus.
- **Vegetarianism and Other High Copper Diets:** Many foods contain a high amount of copper. In particular, vegetarian proteins such as soybeans, nuts, seeds, tofu, avocados, and grains are high in copper content. Fast food hamburgers and other popular foods are soy-based. Soybean protein is coming into wider usage, due to its low cholesterol level and lower cost. Other high copper foods are organ meats, shellfish, wheat germ and bran, yeast, corn oil, margarine, and mushrooms.
- **Occupational Exposure:** Plumbers, welders, machinists, and others who work with copper are at risk for copper toxicity.
- **Dental Appliances:** Copper is used in dental alloys in fillings, crowns, and other appliances.

B. Adrenal Gland Exhaustion and Copper Toxicity: Diminished adrenal activity is perhaps the single most important physiological reason for copper problems today. The reason is that adrenal activity is required to stimulate the production of ceruloplasmin, the primary copper-binding protein. When adrenal activity is insufficient, ceruloplasmin synthesis in the liver declines. Unbound copper begins to accumulate in various tissues and organs, producing copper toxicity.

C. Zinc Deficiency and Copper Toxicity: A widespread zinc deficiency in our population is another critical cause of a copper imbalance. Zinc and copper normally exist in a delicate balance. Zinc is a primary copper antagonist. When zinc is deficient, copper tends to accumulate in various storage organs.

D. Congenital Copper Imbalance: Mothers deficient in zinc, or high in copper, transmit these imbalances to their children through the placenta. Untold numbers of children today are born with a copper imbalance. Often, they suffer from learning problems, developmental disabilities, chronic infections, and other problems.

E. The Copper Personality: The copper personality refers to the observation that certain individuals tendto accumulate copper, perhaps as a physical or psychological mechanism that is adaptive for these individuals.

Toxicokinetics[6,7]

- **Absorption:** Copper is absorbed through the skin, GIT, lungs, and mucous membranes.
- **Distribution:** Normally copper is bound in the blood to ceruloplasmin (95%) and albumin. Organs with a high copper content include the liver, brain, heart, and kidneys. However, excess copper can accumulate in almost every organ of the body.
- **Metabolism:** The main site of metabolism is the liver. In the hepatocyte, copper may either be incorporated into enzymes or form a metallothionein-copper complex in the biliary system.
- **Elimination:** It is excreted through bile and traces are found in saliva and milk. Renal excretion is negligible.

Mode of Action[8]

- Copper inhibits the sulfhydryl groups on enzymes in important antioxidant systems including G-6-PD and glutathione reductase, reducing their free radical scavenging activities.
- Intravascular hemolysis is caused by the inhibition of G-6-PD.
- Copper increases the permeability of cell membranes by inhibiting the NA^+/K^+ ATPase pump.
- Copper intoxication can cause rhabdomyolysis, as it damages human skeletal muscle cells.

Copper Toxicity Relevance to Public Health[9]

- **Acne:** Frequently associated with elevated copper levels or a low imbalanced zinc/copper ratio.
- **Alopecia:** Copper toxicity causes an excessive breakdown of all protein structures, including hair and nails.
- **Anemia:** A high copper/molybdenum ratio may contribute to iron deficiency anemias and possibly cause iron storage disease.
- **Anxiety:** Anxiety states are frequently associated with elevated hair copper levels. This may be due to excessive production of stimulatory neurotransmitters which include catecholamines, epinephrine, norepinephrine, serotonin, and dopamine.
- **Arthritis:** Copper levels in the synovial fluid of patients with rheumatoid arthritis are three or more times as high as normal.
- **Autism:** Both of these metals (copper and iron) are Stimulants for the brain and might produce hyperactivity and/or autism.
- **Candida Albicans Infections:** Copper is a stimulant to oxidative or aerobic metabolism. A copper bio- unavailability, deficiency, or imbalance, often results in a tendency toward yeast infections.
- **Cholesterol:** When copper levels in the blood rise, fat levels decrease. Any contaminant that depresses copper and zinc, such as cadmium in the case of zinc, may cause elevated levels of lipids.
- **Cystic Fibrosis:** Unusually large amounts of copper have been found in the fingernails of infants with cystic fibrosis.
- **Depression:** Mental depression is frequently associated with elevated tissue copper levels. An elevated copper level reduces tissue manganese levels which may result in depression.
- **Diabetes:** is frequently associated with elevated tissue copper levels. Excess copper frequently reduces zinc and manganese levels, thereby interfering with glucose metabolism.
- **Fractures:** Bone fractures are frequently associated with an elevated copper level.
- **Headaches and Migraine:** Elevated copper levels are frequently associated with migraine headaches.
- **Heart Attacks:** A high tissue copper level, by causing a zinc deficiency, predisposes one to hypertension, heart attacks, and strokes.
- **Hypothyroidism:** An elevated copper tissue level is frequently associated with hypothyroidism, particularly when the zinc/copper ratio is greater than 10.00/1. The ideal zinc/copper ratio is 8.00/1.
- **Kidney Disorders:** Kidney dysfunction is frequently associated with a zinc/copper ratio of less than 5.00/l.
- **Libido (Decreased):** A high tissue copper level or a low zinc/copper ratio is frequently associated with a decreased libido.
- **Tooth Decay:** High levels of lead, copper, zinc, and chromium in the body tissues may tend to increase the tooth's susceptibility to decay.
- **UTI:** Elevated copper levels are frequently associated with urinary tract infections.

Clinical Features[10]

1. **Acute Poisoning**

By Ingestion: Metallic taste, increased salivation, colicky abdominal pain, nausea, vomiting- vomitus is bluish or greenish in color, diarrhea, mayalgia, pancreatitis, methemoglobinemia, hemolysis, jaundice, oliguria, renal failure, convulsions, delirium, and coma.

Inhalation: of copper fumes or dust causes Respiratory tract irritation, cough, conjunctivitis, palpebral edema, and sinus irritation, Nasal mucous membrane may show atrophy with perforation and metal fume fever.

Exposure of skin: to copper compounds may cause irritant contact dermatitis, and severe exposure may cause a greenish-blue discoloration of the skin.

2. **Chronic Poisoning**

- Anaemia.
- Abdominal pain.
- Peripheral neuritis.
- Degeneration and atrophy of muscles.
- The greenish line on dental margins of gum (Clapton's line).
- Vineyard sprayer's lung disease: Copper sulphate is used as an insecticide spray in vineyards. During spraying, chronic inhalation of copper sulphate causes this disease.
- Hair shows greenish discoloration.
- Wilson's disease.

- Chalcosis lentis: chronic poisoning may cause deposition of copper in the cornea or lens turning them greenish brown.

Fatal Dose[11,12]

- Copper subacetate: 15 gm.
- Copper sulphate: 20 gm (0.15-0.3 gm/kg).

Fatal Period[13,14]

- 18–24 h, but it may extend to 1–3 days.

Laboratory Diagnosis[15,16,17]

- **Serum caeruloplasmin level:** a value of 35 mg % or less at 24 hours is associated with serious toxicity.
- **Blood copper level:** if this is elevated beyond 1.5 mcg/100 ml, there is a likelihood of serious toxicity.
- **Ammonium hydroxide:** gives a greenish-blue precipitate, which is soluble in excess and forms a blue solution.
- **Rubeanic acid test:** a drop of the neutral test solution on the filter paper is exposed to ammonia. Add a drop of 1% alcoholic solution of rubeanic acid. Spot becomes olive green due to the presence of copper.
- Neutron activation analysis and atomic absorption spectroscopy can detect copper. Merocyanine dye allows copper to be detected using fluorescence spectroscopy.
- **Hair Analysis:** Hair analysis is a rapid, simple screening test that can reveal both direct and hidden copper imbalances. A copper level exceeding 2.50 mg% is considered elevated.

Management[18,19,20]

- **Emetics:** No need to use emetics as vomiting occurs 5-10 min after ingestion.
- **Gastric lavage** with 1% potassium ferrocyanide, which acts as an antidote by forming cupric ferrocyanide (insoluble). If not available, plain water can be used.
- **Demulcents:** Egg white or milk and Sucralfate may help to relieve the symptoms of mucosal injury.
- **Activated charcoal:** Contraindicated.
- Castor oil is given to remove poison from the intestines.
- Patients with methemoglobinemia should be given methylene blue (the dose is 1–2 mg/kg of 1% solution IV over 5 min).
- **The most critical steps:** before chelation therapy is started are (a) Supportive care (b) fluid and electrolyte correction and (c) normalization of vital signs.
- **Chelating agents:** D-penicillamine given in usual doses is very effective. The hydrophilic dithiol chelators DMSA and DMPS are more efficient and suitable alternatives. EDTA or BAL in usual doses is another alternative.
- Allay pain by injecting morphine, and use diuretics, if urine is suppressed.
- Hypotension is treated with fluids, dopamine, and noradrenaline.
- For severe cases associated with anorexia and hematuria, hydrocortisone 50-100 mg IM thrice daily is recommended. However, the routine use of steroids is doubtful.
- Hemodialysis is ineffective but may be indicated in patients with renal failure secondary to copper poisoning.
- **Liver transplantation:** in life-threatening hepatic failure.

Postmortem Findings[21,22]

- The skin may be yellow due to jaundice.
- Greenish-blue froth from the mouth and nostrils.
- The mucous membrane of the mouth and tongue may have a bluish or greenish-blue tinge.
- Internally, some discoloration is present in the mucous membrane of the esophagus and stomach. Caustic burns of the esophagus, and superficial and deep ulcers in the stomach and small intestine may be seen.
- **Stomach***:* Gastric mucosa is congested with desquamation and hemorrhages at places.
- **Small intestine***:* Mucosa (upper part) may show necrosis.
- **Liver***:* Soft and fatty. It shows centrilobular necrosis and biliary stasis.
- **Kidneys***:* It may show acute proximal tubular necrosis. Hemoglobin casts may be seen in the tubules.

Medicolegal Aspects[23,24]

- Suicidal cases are common.
- Accidental poisoning results from eating food contaminated with verdigris (formed from the action of vegetable acids on copper cooking vessels).
- Toxicity may develop from the copper absorbed systemically from the wire used in certain intrauterine contraceptive devices, or from the tubing used in he-

modialysis equipment.

- Rarely, it is used for homicide because of its color and metallic taste.
- Children may swallow copper sulfate crystals attracted by their color.
- Rarely, it is used as cattle poison.
- $CuSO_4$ was used as an antidote for phosphorus poisoning and in wound debridement.

CONCLUSION

Copper toxicity is an important contributor to at least one hundred different signs and symptoms, and disease conditions in public health. Copper toxicity can lead to severe and life-threatening multi-organ dysfunction. In severe cases, early supportive measures are essential in addition to antidotes such as methylene blue in methemoglobinemia and chelating agents such as DMPS to improve the survival of severely poisoned victims. By understanding how copper imbalance comes about and how it causes metabolic dysfunctions, we can prevent many disease conditions in the community. Awareness of copper toxicity is an essential step to the correction and prevention of some of today's most prevalent health problems.

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Source of Support: Nil
Conflict of Interest: None Declared

How to cite this URL: Vishal G. Mali & Rajesh Upadhyay: An Effect of Copper Toxicity in Relevance to Public Health. International Ayurvedic Medical Journal {online} 2022 {cited October 2022} Available from: http://www.iamj.in/posts/images/upload/2665_2671.pdf