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ARTICLE

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PATHOPHYSIOLOGICAL IMPACTS ARISING FROM DISRUPTION IN COPPER HOMEOSTASIS

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Copper is an essential trace element and it plays vital roles in cellular metabolism.Copper has a profound role in boosting the immune system and fighting against infections. Disruption of copper homeostasis invites various pathophysiological consequences such as cardiovascular system disorders, connective tissue and neurobiological disorders.Recent studies highlight the association of copper in disrupting lipid homeostasis such as non-alcoholic fatty liver disease (NAFLD). Despite these findings significant questions remain unanswered. More sensitive biomarkers for copper status are needed to be sought out. Further investigations on these queries will uncover more specific details of copper metabolism in humans.

Introduction

A lion's share of the world's population is far from improved global nutritional health benefits due to consuming macronutrients adequate in amounts but having been suffering from the want of micronutrients such as copper[1]. Copper was first found in marine plants and invertebrate fauna and was later described in human tissues[2]. It serves as co-factor for various copper containing metalloproteins indispensible for life. Copper is transported to the peripheral tissues after binding with the copper binding protein ceruloplasmin in the liver. Approximately 50% of copper is excreted in the bile and the remaining is secreted through other gastrointestinal secretions. The pathophysiological role of copper was witnessed for the first time in Wilson's Disease[2]. It was later identified as a mutation in the ATPase copper transporting beta (*ATP7B*) gene[2]. The ATPase is responsible for the excretion of copper in the bile. Copper deficiency invites developmental bone malformation[3]. Its depletion also invites anemia[2]. This relationship became evident after four decades during the first description of Menkes Disease (MD).Systemic copper deficiency leads to defective intestinal copper absorption due to mutations in the copper transporting ATPase alpha (*ATPase7A*) gene[4]. Based on these studies it can be amply demonstrated that copper is a quintessential nutrient in the human diet.

On the contrary, the presence of copper beyond the need for normal physiology can invite devastating effects to the human body. Free copper ions can cause damage to cellular macromolecules[5,6]. The balance between the uptake and efflux of Cu^{2+} determines the availability of the copper ions in the intracellular environment. When present in excess, the redox active metal ion invites the oxidative stress response and damages cellular macromolecules. It has been reported that ingestion of more than 1g of copper sulphate initiates the symptoms of copper toxicity[7]. Primary copper toxicosis arises from an inherited defect in cellular metabolism and the secondary effect arises from higher copper retention resulting from high intake or reduced excretion[7]. It has also been reported for consumption of acidic foods in uncoated copper cookware or consuming drinking water with copper overload[7]. The present review focuses on the pathologic consequences arising from copper toxicosis along with presenting some glimpses of the beneficial roles of this essential trace element.

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Biochemistry of Copper

Copper is a group 11 metal having atomic number 29 and atomic mass ~63.5Da. Copper exists in two biological ionic forms Cu^{+} (cuprous) and Cu^{2+} (cupric). Cuprous ion is water insoluble and usually exists as complexes with other biological macromolecules. Copper is redox active and switches between these two oxidation states during enzymatic catalysis. Copper resides within the copper binding site in a protein structure and is responsible for single electron transfer with oxygen[7]. Among the various naturally available radioisotopes of copper ^{67}Cu (half life ~70h) and ^{64}Cu (half life ~ 13h) are frequently used in pathway tracking of copper in animal models[7]. The isotopes have limited usage in humans owing to its high energy emissions and short half lives. The two stable isotopes of copper ^{63}Cu and ^{65}Cu are most commonly used in investigating metabolic flux of copper and copper homeostasis in humans.

Copper Exposure: A Brief Overview

A typical balanced diet provides ~1.2-1.3 mg/day of copper intake with a daily absorption of 0.8 mg by the duodenum [7]. After being absorbed it is then transported via the portal circulation to the liver. Within the hepatocytes co-translational incorporation of copper into ceruloplasmin (CP) or other copper binding proteins takes place. Approximately 70–89% of the copper linked to CP, depending on the mammalian species, is not easily exchanged within cells, meaning that this is not the transportable form. Transportation copper is basically atomic copper that exits liver and binds to serum proteins and gets supplied to the tissues. Daily copper intake is indispensible owing to low body copper storage. A little amount of copper chelated to the cysteine rich protein metallothionein (MT) can be released slowly according to the metabolic demand[8]. Metallothioneins also show a protective role against copper induced oxidative stress when the homeostasis gets disturbed[7]. Biliary excretion of excess copper is mediated by ATP7B copper transporter. Body loses ~1mg/day of copper as unabsorbed and excreted copper. Copper homeostasis is regulated by regulation of both the rate of intestinal absorption and excretion. Higher ingestion of copper suppresses intestinal absorption and enhances biliary excretion and the opposite phenomenon occurs in case of copper depletion. Figure 1 provides some of the outlooks of copper poisoning in human.

Effects of Inadequate Exposure: **Acute Exposure:** Acute exposure of copper result into gastrointestinal anomalies. After reaching the stomach complexed with copper binding biomolecules it interacts inefficiently with the mucosa than ionic copper. The phenomenon explains that gastrointestinal manifestations from copper toxicity don't come from food intake but from contaminated water where ionic copper exists[1]. Acute toxicity primarily induces nausea, vomiting, diarrhea but sufficiently higher doses can invite multiple organ failure and death. Copper ions after stimulating the receptors stimulates the vagus nerve and bring about nausea. Higher copper doses end up with vomiting by stimulating vomiting centre in the hypothalamus[1].

Chronic Exposure: The deleterious effects of copper become much more prominent in disease states such as Wilson's disease[1]. It is an autosomal recessive disorder due to mutation in an ATPase called Wilson protein (ATPase7B). The defective results into copper accumulation in the liver owing to its inability to bind ceruloplasmin and biliary export. Effects of chronic exposure to copper have not been well understood in healthy individuals[1].

Copper Homeostasis

Systemic View: Mammalian system harbors adaptive mechanisms to prevent both copper deficiency and overload. The primary regulation occurs at the intestine when it absorbs copper to meet the body demands. Only a little amount of enteric copper is absorbed and especially fractional absorption increases during higher copper intake[9]. Increasing copper intake decreases the percent absorption. Higher intake also results into copper binds with MT in the enterocytes preventing release of copper in the portal blood circulation along with increase in biliary excretion. Daily copper intake of less than ~0.4mg/day doesn't invite such physiological adaptations in maintaining homeostasis[10]. Chronically excessive intake dampens the regulatory mechanisms of copper homeostasis.

Molecular View: Genetic variations which influence gene expression levels and protein function also have a keen influence on dietary copper requirement. The regulatory mechanisms that influence copper homeostasis probably don't directly modulate the rates of transcription initiation. A recently identified copper responsive transcription factor (ATOX1) has been identified to be transported in the nucleus upon higher intracellular copper levelswhich regulates the expression of the antioxidant enzyme SOD3[11] (Figure 2). Copper homeostasis is primarily regulated at the post translational level[12]. According to this postulate the m-RNA expression for the cuprotransporters such as ATP7A, ATP7B and CTR1remains unaltered by variations in copper intake.

Rather the import/export of copper seems to be primarily regulated by copper dependent intracellular trafficking of the cuprotransporters.

Systemic Effects of Copper Imbalance

Cardiovascular Effect: Multiple lines of evidences from animals, cell culture and human genetics have demonstrated the disruption in copper metabolism invites heart disease and it is the predominant cause of mortality in the United States. Copper deficiency lead to pathological changes in cardiovascular physiology as has been noted in experimental animals. Abnormality ranges from electrical, mechanical, anatomical and biochemical malfunctioning. Prolonged copper deficiency leads to hypertrophic cardiomyopathy and onset of ischemic heart disease in experimental mice models[13]. Hypercholesterolemia and hypertriglyceridemia have also been reported in rats suffering from copper deficiency[14]. The cardiovascular anomalies arising from copper deficiency are quite distinct from atherosclerotic heart disease as observed in humans. But extensive literature on the cardiovascular anomalies of other animals can shed light on what occurs in humans owing to copper deficiency. Latest experimental evidences have confirmed copper depletion to be a factor of cardiovascular disease in humans[2]. A relationship between low serum copper concentrations and cardiac arrhythmias and ischemic heart disease has been documented[15]. Ample amount of copper supplementation supresses the risk from myocardial infarction which is especially evident in obese individulas, smokers and patients suffering from hypertension and diabetes.On the other hand copper overload has also been associated with the risk of cardiovascular disorders. Copper is a redox active metal and induce production of superoxide radicals at higher dosage [2]. Several studies have marked the correlation between coronary heart disease and increased serum copper concentrations. Elevated copper concentrations in the blood are linked to both increase in bound (ceruloplasmin bound) and free copper known as atomic copper. The atomic copper interacts with various serum ligands such as albumin. Atomic copper when present in excess creates redox imbalance and subsequent pathophysiological conditions[2]. The situation leads to atherosclerotic heart disease, a disease from chronic inflammation. Ceruloplasmin being an acute phase protein and hence shows elevated serum concentrations during infection and inflammation. Eventually it can be stated that more study is required to elucidate whether low or high copper concentrations is linked with increased cardiovascular disorders.

Effect on the Immune System: Copper is required for the normal development and function of the immune system although the mechanisms have not properly been understood. Individuals suffering from copper deficiency are prone to increased risk of infection which indicates towards the importance of copper for the proper functioning of the immune system[16]. Serum copper deficiency invites neutropenia, leucopenia, osteoporosis, arthritis and other bone defects[17]. Copper deficiency invites decline of macrophage and lymphocyte population and also neutropenia[2]. It also brings about more severe impact on neonatal immune function which is evident from frequent occurrence of Menkes Disease in infants suffering from copper deficiency. Supplementation of copper increases the phagocytic activity of immune cells of infants suffering from copper deficiency[2]. Low copper availability suppresses the activity of copper containing metalloenzymes in blood cells[18]. Copper also plays important roles in the proper functioning of the innate immune response against bacterial infections which is due to copper transporting ATPase (ATPase7A) in macrophages. A relationship of copper availability, immune system and SARS-CoV-2 and COVID19 has also been investigated[19].

Osteopathology: Genetic deficiency of acquiring copper invites connective tissue disorders such as bone defects and osteoporosis. The prime target behind this malfunctioning is a cuproenzyme named lysyl oxidase (LOX) taking part in collagen biosynthetic pathway. Infants suffering from copper deficiency are prone to develop abnormal bone morphologies similar to connective tissue especially osteopathologies appearing in vitamin C deficiency which impairs collagen cross linking and stabilization. Consuming copper lower than RDA recommended limit (0.7mg/day) for two months invites osteoporosis. Copper supplementation (3-6mg/day) for six weeks didn't emerge the biological indicators of malfunctioned bone health[20]. Eventually in assessing the relationship between copper deficiency and bone physiology it can be said that the effect of dietary copper supplementation will depend on the accurate determination of the copper nutritional status of the participants of clinical trials.

Neurodegenerative Disorders: Copper after reaching the blood brain barrier (BBB) with binding proteins, the ionic copper not the bound copper-protein complex, crosses the BBB and eventually distributes to brain parenchyma and the cerebrospinal fluid. Lower serum copper concentration has been reported to have declining cognitive power which may be circumvented by iron[21].

Dysregulated copper homeostasis invites Alzheimer's disease (AD)[2]. Both low and high copper invites cognitive decline leading towards Alzheimer's disease (AD) in adults. Patients suffering from AD have increased blood levels of highly reactive free copper which is highly redox active[22]. Interaction of excess redox active copper with â-amyloid peptides has been evidenced which promotes the development of pathological plaques in the AD patient's brain. Polymorphisms of the *ATP7B* gene may increase in AD risk. The ATPase exports copper but with lower efflux activity [2]. ATP7B is required for excretion of copper from the liver and is required for the production of ceruloplasmin (CP). Disabled biliary copper transport leads to copper accumulation in the liver and eventually surpasses its activity of storing copper. The excess copper is emitted in the bloodstream raising the copper levels in serum to pathologic level and increases copper accumulation in the brain. Increased ionic copper and low CP activity owing to low CP ferroxidase activity increases oxidative stress and make the victim prone towards Alzheimer's disease. Patients suffering from Wilson's disease (WD) show progressive copper accumulation in the liver, brain and cornea and subsequently redox active copper can cause tissue damage [2]. High accumulation of copper in the brain can cause neurological disorders, ocular copper accumulation (Kayser-Fleisher rings) and abnormal ocular movements[2].

Impairment in Lipid Metabolism: Copper homeostasis also affects lipid homeostasis. Altered copper homeostasis has been reported in obese individuals. Depletion of dietary copper increases body fat and perturbs lipid metabolism[23]. Copper depleted rats accumulate long chain fatty acid enriched triglycerides in various tissues. Inflammation, fibrosis and hepatic steatosis have been observed in copper depleted mice models mirroring human non-alcoholic fatty liver disease (NAFLD)[24]. NAFLD patients also suffer from low hepatic copper levels leading to higher fat deposition in the organ called steatosis. Ceruloplasmin level is also low in serum along with low copper concentration. Insufficient copper levels have also been observed in murine NAFLD models[25]. Higher copper levels induce fat mobilization and depletion of fat storage[26]. The influential effect of copper on lipid homeostasis has been observed in experimental animals. Copper treatment has led to decrease in subcutaneous fat in steers, increased lipolysis in sheep adipose tissue and decreased fat deposition in rabbits[27]. Thus both reduced and excess copper can bring about changes in lipid homeostasis but in a reversible manner. The sorting of detailed mechanism of action needs further studies.

Summary

Various mechanisms for the biological effects of copper have been deciphered in the last few decades but much remains to be studied further about its physiological and pathophysiological effects. A few possibilities need to be explored. The most frequently assessed biomarkers in assessing the copper status in human physiology take into account the blood copper content, red blood cell SOD activity and circulating ceruloplasmin (CP) levels. However, these biomarkers can give misleading results such as the increase in the CP levels has been observed during pregnancy and other pathologic states not related to copper imbalance. These biomarkers hardly predict other pathologic states, arising from sub-clinical copper deficiencies. More sensitive biomarkers are needed to be sorted out. More definitive evidence is needed to be provided to elucidate whether copper deficiency or excess copper or both play the significant role. Latest insights provide some of the glimpses of adverse impacts of copper on lipid metabolism (NAFLD). The mechanisms of interference in lipid metabolism by low or high copper remain to be elucidated in animal models and in human. The role of copper in heme biogenesis is well documented but its underlying mechanism remains to be elucidated. The relationship between copper deficiency and ischemic heart disease is also open for future study. Lastly, it can be summarized that novel and sensitive biomarkers needed to be discovered related to copper biology and its pathophysiological effects in human system.

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References

1. M. Araya,M. Olivares,F. Pizarro, *Int. J. Environ. Heal.* **1:** 608–620 https://doi.org/10.1504/IJENVH.2007.018578 (2007)
2. J.F. Collins, *Advances in Food and Nutrition Research.* Elsevier Inc.**1st ed** https://doi.org/10.1016/bs.afnr.2021.01.005 (2021)
3. Z. Tümer,L.B. Møller,*Eur. J. Hum. Genet.***18:** 511–518. https://doi.org/10.1038/ejhg.2009.187 (2010)
4. T.M. Allen,A. Manoli,R.L. LaMont,. *Clin. Orthop. Relat. Res.* **16:** 206–210. https://doi.org/10.1097/00003086-198208000-00037 (1982)
5. H. Tapiero, D.M. Townsend, K.D. Tew,*Pharmacother*, **57:** 386–398. https://doi.org/10.1016/S0753-3322(03)00012-X (2003)

6. S. Oe, K. Miyagawa, Y. Honma, M. Harada , *Cell Res.* **347:** 192–200. https://doi.org/10.1016/j.yexcr.2016.08.003 (2016)
7. A. Royer, T. Sharman,*Copper Toxicity - StatPearls - NCBI Bookshelf* (2022).
8. J. Calvo, H. Jung, G. Meloni,*IUBMB Life* , **69:** 236–245. https://doi.org/10.1002/iub.1618 (2017)
9. L.J. Harvey,J.R. Dainty, W.J. Hollands, V.J. Bull, J.H. Beattie, T.I.Venelinov, J.A. Hoogewerff, I.M. Davies, S.J. Fairweather-Tait, *Am. J. Clin. Nutr*. **81:** 807-813. https://doi.org/10.1093/ajcn/81.4.807 (2005)
10. D.M. Danks, P.E. Campbell, J. Walker-Smith, B.J. Stevens, J.M. Gillespie, J. Blomfield, B. Turner, *Lancet*,299:1100–1103. https://doi.org/10.1016/S0140-6736(72)91433-X (1972)
11. Itoh S, Ha WK, Nakagawa O, Ozumi K, Lessner SM, Aoki H, Akram K, McKinney RD, Ushio-Fukai M, Fukai T. Novel role of antioxidant-1 (Atox1) as a copper-dependent transcription factor involved in cell proliferation. J. Biol. Chem. 2008; 283: 9157–9167. https://doi.org/10.1074/jbc.M709463200
12. S. Itoh, K. Ozumi, H.Won, O. Nakagawa, R.D. Mckinney, R.J. Folz, I.N. Zelko, M. Ushio-fukai, T. Fukai, *Free Radic. Biol. Med.***46:** 95–104. https://doi.org/10.1016/j.freeradbiomed.2008.09.039 (2009)
13. J.R. Prohaska, A.A. Gybina, *J. Nutr*. **134:** 1003–1006. https://doi.org/10.1093/jn/134.5.1003 (2018)
14. P.V.E. Berghe, L.W.J. Klomp, *J. Biol. Inorg. Chem*. **15:** 37–46. https://doi.org/10.1007/s00775-009-0592-7 (2010)
15. Y. Liu, J. Miao, *Nutrients*. **14.**https://doi.org/10.3390/nu14030700 (2022)
16. J. Liu, C. Chen, Y. Liu, X. Sun, X. Ding, L. Qiu, P. Han, *Exp. Biol. Med*. **243:** 1141–1152. https://doi.org/10.1177/1535370218813988 (2018)
17. H. Aliabadi, **70:** 1163–1166. https://doi.org/10.1016/j.mehy.2007.09.019 (2008)
18. J.J. Dinicolantonio, D. Mangan, J.H.O. Keefe,**5:** 1–8. https://doi.org/10.1136/openhrt-2018-000784 (2018)
19. H. Wen, X. Niu, L. Hu, N. Sun, R. Zhao, Q. Wang, Y. Li, *Front. Cardiovasc. Med*, 9: 1–12. https://doi.org/10.3389/fcvm.2022.942000 (2022)
20. B. Bagheri, N. Akbari, S. Tabiban, V. Habibi, V. Mokhberi,*Niger Med J*.**56:** 39–43. https://doi.org/10.4103/0300-1652.149169 (2015)
21. Y. Liu, J. Zhu, L. Xu, B. Wang, W. Lin, Y. Luo, *Front. Mol. Biosci*.**9:** 1–6. https://doi.org/10.3389/fmolb.2022.1065265 (2022)
22. M.L. Failla, R.G. Hopkins, *Nutr. Rev.* 56: S59-S64. https://doi.org/10.1111/j.1753-4887.1998.tb01646.x (1998)
23. A. Andreou, S. Trantza, D. Filippou, D. Filippou, N. Sipsas, S. Tsiodras, **34:** 1567–1588. https://doi.org/10.21873/invivo.11946 (2020)
24. A. Baker, L. Harvey, G. Majask-Newman, S. Fairweather-Tait, A. Flynn, K. Cashman,*Eur. J. Clin. Nutr.***53:** 408–412. https://doi.org/10.1038/sj.ejcn.1600763 (1999)
25. Y.M. Choe, G.H. Suh, B.C. Lee, I.G. Choi, J.H. Lee, H.S. Kim, J.W. Kim, *AgingNeurosci*.**14:** 1–10. https://doi.org/10.3389/fnagi.2022.811117 (2022)
26. A. Rembach, D.J. Hare, M. Lind, C.J. Fowler, R.A. Cherny, C. McLean, A.I. Bush, C.L. Masters CL, B.R. Roberts, *Int. J. Alzheimers. Dis.***2013:** 623241. https://doi.org/10.1155/2013/623241 (2013)
27. J.L. Burkhead, S. Lutsenko, In Tech Open Limited. https://doi.org/10.57772/51819 (2013)