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A Theory on the Impact of Copper and Micronutrients Against COVID-19 in Humans

Caitlin A. Connor, DAOM, PGDip, AMP, EHP-C.[1,2,*]

[1]Health Sciences Research, Rewley House, University of Oxford, UK.

[2]Principle Investigator, Earthsongs Holistic Consulting.

Corresponding author:

Caitlin Connor, Health Sciences Research, Rewley House, University of Oxford, UK.

Principle Investigator, Earthsongs Holistic Consulting.

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Jigar Modi, Postdoctoral Fellow, Neuroscience, Florida Atlantic University.

Abstract

Copper (Cu) has a strong impact on the function of the immune system through several different pathways. These impacts include helping the function of monocytes, neutrophils, and macrophages, and enhancing Natural Killer cells' activities. Cu also has a role in antimicrobial properties and inflammatory response. It is also important for IL-2 production and response, which is a component of adaptive immune cells. Additionally, Cu has multiple roles in both proliferation and differentiation of T cells and is involved in the production of antibodies. Cu deficiency can even lead to "increased viral virulence"[1]. Copper has a long history of use in medicine, and has continued to be used for purification of water, including use in hospitals to prevent legionnaires disease. The CDC pre released information on a study completed in March 2020 on the lifespan of COVID-19 on different surfaces which included its lifespan on copper, where it was completely dead within 4 hours. In addition, "Several reports demonstrated that Cu deficiency weakens the human immune response" [2]. Given the multiple avenues of impact, it has been suggested that Cu supplementation, within recommended levels, be given to individuals who are low in Cu to help them fight off COVID-19. It is also possible that Cu supplementation, within recommended levels, may help prevent COVID-19 infection, or help individuals who are not low in Cu to fight off COVID-19 infection. However, dosage would have to be carefully managed, as excess levels of Cu can lead to both neurodegenerative and neurodevelopmental diseases.

Introduction

The duality of copper is important to remember when investigating its effects on the human body. In excess, copper can cause severe negative health issues, which include "cirrhosis and chronic hepatitis, neurodegeneration, parkinsonian features, seizures, and psychiatric symptoms such as psychosis" [3]. In contrast to these issues "...copper is fundamental to life as we know it, and that there can be no such life without copper" [4]. A number of necessary processes in the human body are mediated by copper. Included in these are several aspects of immune function. Copper also has a long history of use as an antimicrobial agent, both internally and externally [5], including recent evidence of its impact on the length of survival of the COVID-19 virus on surfaces [6]. While research on the impact of copper directly on SARS-CoV-2 is limited at this time, research on similar and related viruses can be used to guide theory. "Furthermore, in vitro studies show that copper ions block a fundamental protein for SARS-CoV-1 replication. Hence, copper has antiviral properties acting at two levels: enhancing the components of the immune system to fight against infections and by direct contact with virus" [7]. This combination suggests that copper may help individuals who have been exposed to COVID-19 to fight off infection.

SARS-CoV-2

Coronaviridae are a family of viruses identified by their "contained RNA surrounded by a membrane composed of "spike"-shaped proteins" [8]. "The crown-like appearance of these surface "spike" proteins gave the virus family the name - "corona" being Latin for crown" [8]. One of these viruses, specifically SARS-CoV-2, was declared a pandemic by the WHO on March 11, 2020 [8]. SARS-CoV-2 spike proteins are used to attach to cells at the angiotensin-converting enzyme 2 [ACE2) receptor[8]. This receptor is the same location used by SARS-CoV [8), suggesting that interventions that were successful against SARS-CoV infection might also work against SARS-CoV-2. Once SARS-CoV-2 has attached to a cell it "it integrates its RNA into the cell's own replication machinery, facilitating propagation of the virus" [8]. "Symptoms of the virus are similar to MERS and SARS, and include fever, cough, and shortness of breath", though COVID-19 has proven to be "significantly more infectious than SARS and MERS in terms of human-to-human transmission" [8]. The difference between SARS and COVID in viral load at symptom development, meaning that COVID can be transmitted prior to symptom development, also makes it more difficult to contain [8].

Background

Copper has been shown in the past to attack multiple different types of viruses [5, 9, 10]. These virus types have specifically included SARS-CoV-1 [7], HIV, Polio [5], type A influenza virus [1], and M. tuberculosis, where the immune system responded by creating an overload of copper and zinc in the phagosome [10]. Copper has also been shown to decrease infectiousness within two minutes in a Norovirus strand [9]. The CDC prereleased information on a study completed in March 2020 on the lifespan of COVID-19 on different surfaces [6]. This included the lifespan on copper, where the virus was completely dead within 4 hours [6].

In addition to the direct effects of copper on viruses, copper appears to have a beneficial effect on the immune system. "Copper has previously been implicated in the regulation of immune responses..." [11]. It should also be noted that, aside from decreasing the microbial burden itself, copper has also demonstrated an antimicrobial effect on its surroundings, even outside of the immediate environment. This effect has been tested and remained consistent for 21 months [12] "The levels of antimicrobial activity of the metallic copper surfaces were equivalent throughout the course of the trial" [12]. "The most surprising finding was the 64% decrease in MB between the preintervention and intervention phases in the control rooms" [12].

History

Copper has a long history of use in medicine, starting with use in the purification of drinking water and the treatment of burns in Egypt in 2000 BC [5]. The use of copper for the purification of water continued through Greece in 400 BC to early American pioneers, who placed copper coins in water casks, and in WWII, where Japanese soldiers used pieces of copper in water bottles to prevent dysentery [5]. It was also used by the Greeks in 400 BC for pulmonary diseases, a treatment that was repeated in the 18th century, when it became widely used clinically for both lung and mental issues [5]. The Roman Empire used cooking utensils made from copper to prevent disease spread [5]. Skin conditions were treated using copper oxide, as well as malachite, by the Aztecs, and are still treated using copper sulphate by some residents of Africa and Asia [5]. It has continued to be used for purification of water to this day, including use in hospitals to prevent legionnaires disease [5] It also has EPA approval for use as an antimicrobial surface [5]

Biochemistry- Copper's Effects on Viruses

Copper has been shown in the past to have a negative impact on multiple different types of viruses [5, 9, 10]. Copper ions have been shown to directly attack viruses in two different ways, using two different types of ions. The first, Cu(II), attacks the capsid barrier [9]. This starts with the virus's receptor sites, immediately limiting its ability to infect individuals even prior to virus death [9]. This process has been shown to decrease infectiousness within two minutes in a Norovirus strand [9]. Research in 1993 by Sagripanti et al. showed that after 30 minutes, 99% of the virus was inactivated in vitro, caused by Cu(II) [13]. The second ion, Cu(I), goes after the genome [14]. Borkow [5) showed that one of the nucleic acids forms covalent bonds with copper, and in the process divides the genome into pieces [5]. This nucleotide can occur as often as every three nucleotides [5), which means that the genome divides into progressively smaller sections over time [14]. This has been seen to start within 15 minutes and leaves no viable virus within 2 hours [9]. The DNA damage has been found to occur even with nanoparticles of copper, and not just with solid objects [15]. Cu(II) also "can inhibit RNA polymerase activity by more than 60%, with copper exhibiting the strongest effect compared to other metal ions" [13]. The damage to viral DNA and RNA also means that the genomic information will not be available for other viruses to integrate and mutate [14]. Research has also suggested that enveloped viruses are more strongly affected by Cu(II) inactivation, and that RNA and lipids may increase sensitivity of viral particles to this inactivation [13]. It is very important to remember that the covalent bonds formed between copper and nucleic acids also means that other, stronger, bonds can distract the copper molecules [5]. These include glutathione and cysteine [5]. The human body has been shown to use particularly high concentrations of specific micronutrients, including copper, internal to various immune cells, to destroy viral particles [16]. This specifically includes macrophages [16]. In addition to these very direct attacks on the virus itself, research suggests that copper can interfere with proteins which produce functions that are important for the virus [13].

Biochemistry- Copper's Effects on the Human Body

More research still needs to be done on the mechanisms of copper in the human body, but the research that has been done so far has resulted in some interesting findings. The first is that there is almost no free or unused copper present in the human body. It is usually bound to another substance, and usually for a specific purpose. The current research suggests that copper is most commonly a cofactor for either electron transport proteins or specific enzymes that are involved in antioxidant or energy metabolism [4], though copper deficiency also appears to affect every cell, as "copper is required for the assembly and activity of complex IV of the mitochondrial respiratory chain" [3] and impairment of this chain due to copper insufficiency appears to produce enlarged mitochondria, as is seen in Menkes disease [3]. "Cuproenzymes are involved in oxidizing metals and organic substrates and produce a wide array of metabolites, neuropeptides, pigments and many other biologically active compounds" [16]. In addition to these functions, copper has been linked to apoptosis and autophagy, which "has been demonstrated to have an antiviral response to viral oxidative stress" [13]. This response helps to limit viral infection [13]. "The copper/autophagy interconnection opens potential therapeutic application studies and clinical development of copper to target COVID-19 infection" [13]. "The functions of these copper dependent enzymes alone make it abundantly clear that copper is fundamental to life as we know it, and that there can be no such life without copper" [4].

Copper seems to have a role in almost every, if not every, stage of immune response [1]. "Copper can boost the host's immune system response against pathogens, exhibiting strong antibacterial, antifungal, antiviral and anti inflammatory (*sic*) effects" [13]. Ongoing research has "established that the complex, integrated immune system needs multiple specific micronutrients, including vitamins A, D, C, E, B6, and B12, folate, zinc, iron, copper, and selenium, which play vital, often synergistic roles at every stage of the immune response" [1]. The first stage of the immune response includes physical and biochemical barriers to entry. While copper does not have a clear role in this stage, it does have an impact on the proper formation and function of connective tissue and collagen maturation, both of which are likely to impact the physical barrier aspects [4]. Once this stage has been bypassed, the role of copper becomes much clearer. The second stage of immune response is one of innate immunity. This stage primarily consists of an inflammatory process involving phagocytes, Natural Killer (NK) cells, and antimicrobial substances in blood serum response [1]. Copper specifically "has intrinsic antimicrobial properties that destroy a wide range of microorganisms" [1]. Once the anti microbial defenses have been bypassed, NK cells are activated [1]. Once infected cells are destroyed by NK cells, neutrophils and macrophages migrate to the area and destroy any released microbes through phagocytosis [1]. Copper specifically helps the function of monocytes, neutrophils, and macrophages, and enhances NK cells' activities [1]. Phagocytosis also produces Reactive Oxygen Species (ROS) or a respiratory burst, where copper is key in the defense against damage from both. Copper can also trigger the formation of an ROS specifically to kill pathogens [1]. The inflammatory response is triggered by a large number of different types of immune factors, as well as an increase in blood flow to the area to dilute any external factors that may have entered through the trauma [1]. It also helps to repair the local damage. As part of this inflammation response, "copper is important for the production and response of IL-2 to adaptive immune cells and accumulates at the sites of inflammation" [1]. Metallothioneins containing copper are also among the oxygen radical scavengers released at inflammation sites by immune cells [4].

The third step in an immune response takes more time to implement, as it requires immune cells to recognize the pathogen and replicate prior to effectiveness. These cells are sorted into two main categories, T cells and B cells. Copper is specifically important to the differentiation and proliferation of T lymphocytes, a subcategory of T cells [1]. Once immune cells have recognized a pathogen and T or B cells have been implemented, future immune responses are much faster [1]. Copper also plays a role in the signal that activates T cells, as well as T-cell proliferation and the activity of NK immune cells [1]. Additionally, copper is involved in the production of antibodies, which neutralize the invading agent and draw phagocytes to the area [1]. It even appears that copper can trigger both apoptosis and autophagy, both of which protect cells [13]. Copper deficiency can even lead to "Increased viral virulence" [1] as well as "less effective immune responses against infections" [7]. "Consistent with this evidence, it has been hypothesized that the optimal state of plasma copper levels can increase both innate and adaptive immunity, even exerting an effect as a preventive and therapeutic factor against COVID-19" [7].

Changes in Copper Amounts in the Body due to Infection

An interesting factor in the human immune response as relates to copper is that a recognized mark of an infection, regardless of the type, is a clear and continuing increase in copper in blood serum [16]. It is likely that this is due to an increase in ceruloplasmin levels in the blood as a reaction to inflammation [13, 16]. An increase in IL-6 levels has also been shown to increase the amount of ceruloplasmin in the blood [13]. "Since one molecule of ceruloplasmin binds 6 atoms of copper, even a modest increase in ceruloplasmin during infection can account for a substantial elevation in serum copper" [16]. It has been suggested that the increase in copper may be an attempt to decrease inflammation, and that inflammatory diseases may be due to an insufficient anti-inflammatory response due to low levels of stored copper [13]. In contrast to the changing levels of copper due to infection, studies analyzing copper absorption have shown that levels of copper absorption remain the same after 2.5 mg. [13]. This suggests that there is no benefit to consumption beyond that point, even during an active infection.

Zinc

The T cells specifically look at antigen markers that code individual cells as self or non-self. Zinc has a fair amount to do with regulation of this stage of immune function and maintaining immune tolerance through triggering the development of Regulatory T cells (Treg cells) and reducing inflammatory factors [1]. Even "The proliferation of cytotoxic T cells is induced by zinc" [1]. "Microarray analysis of T-lymphocyte population changes in moderate zinc deficiency showed changes in expression of 1200 genes related to the proliferation, survival, and response of T-cells" [1]. It is even "essential for intracellular binding of tyrosine kinase to T cell receptors, required for T cell development, differentiation, and activation; induces development of Treg cells and is thus important in maintaining immune tolerance" [1]. Zinc also decreases inflammation by decreasing the development of Th17 and Th9 cells and impacts the "generation of cytokines such as IL-2, IL-6, and TNF-alpha" [1]. Unfortunately zinc also binds to the same transport molecules that copper does, which means that an increase in zinc also inhibits copper absorption. "Abnormally high concentrations of Zn(I1) (30-100:l) and perhaps also of Fe(II/III) directly or indirectly inhibit uptake and transfer of copper from the diet to the blood" [4]. This is even used as a standard treatment for high levels of copper in Wilsons disease [3].

Negative Effects of Insufficient Copper

There are negative impacts that arise from copper levels in the human body being either too low or too high. These impacts need to be understood when discussing the use of copper for health support. The impact of a sufficient lack of copper has been shown to include a lack of collagen maturation and improper elastic fiber sheathing of blood vessels [4]. Copper is even critical to nerve signaling and stress responses through its enzymatic impact on the dopamine-norepinephrine-epinephrine cycle [4]. Severe copper deficiency has been shown to impair production of norepinephrine in the brain, leading to accumulation of dopamine in specific areas [4]. Animal studies have even suggested that both the synthesis of dopamine and myelination during development are copper dependent [4]. Copper may also be able to reduce pain due to binding with enkephalin peptides, and has an impact on new tissue development through angiogenesis [4].

It has been previously established that certain nutrients are critical to the maintenance of the immune systems normal activity, including avoiding and defeating infections. "Specifically, the European Food Safety Authority (EFSA) evaluated and deems six vitamins (D, A, C, Folate, B6, B12) and four minerals (zinc, iron, copper and selenium) to be essential for the normal functioning of the immune system, due to the scientific evidence collected so far" [7, 17]. This raises the question of how low these vitamins and minerals would have to be to cause a decrease in immune function [1]. The research on this to date has had mixed results, but there is evidence that the supplementation of these micronutrients that have documented immune support functions "may modulate immune function and reduce the risk of infection" [1]. This is especially important as many individuals, even in industrialized countries, often do not get enough of these micronutrients from their diet [18]. This has specifically been observed with copper, among other nutrients [7]. Surveys studying the diet in Europe have previously found widespread suboptimal intakes of these micronutrients, specifically including copper, with a range of 11% to 30%, including a high prevalence of insufficient intake in the elderly [7]. "Furthermore, suboptimal copper intake (even without reaching critical deficiency) is associated with decreased T-cell proliferation and abnormalities in macrophage phagocytosis" [7].

Unfortunately, there is currently little information on what level of deficient micronutrient status would constitute suboptimal levels, and the health effects at that level of deficiency [1]. It should also be noted that this will vary between different populations [1]. This also means that there is insufficient information to establish optimal levels for the maintenance of immune function in differing individuals [1]. The problem is particularly complicated by both the relatively stable absorption levels of copper combined with the tendency for copper levels in serum to rise with infection. It is very important to note that "the European countries worst hit by the pandemic show population% with suboptimal intake of vitamins and minerals that are important to the immune system" [7]. In combination with this, "a lower population% with covered needs of vitamin C, iron, and copper is related to higher relative mortality rates from COVID-19. Accordingly, the UK presents a large population% with suboptimal intake for these three micronutrients" [7].

Negative Effects of Excess Copper

Too much copper also has serious negative effects on the human body. For example, "ATP7B mutations lead to systemic accumulation of copper due to impaired excretion by the liver" [3], and cause a subtype of neurodegenerative and neurodevelopmental diseases [3]. The damage done by excess copper is shown the most in the brain and liver [3]. Specific symptoms of liver toxicity, as commonly demonstrated by individuals with Wilson disease, include "cirrhosis and chronic hepatitis, neurodegeneration, parkinsonian features, seizures, and psychiatric symptoms such as psychosis" [3]. "Copper is a powerful trigger of Parkinson's molecular pathology including alpha-synuclein aggregation as well as oxidative damage of proteins, lipids, and mitochondria" [3]. If levels of copper get high enough it can also be deposited in the eye, which creates a halo around the cornea called a Kayser–Fleischer ring [3]. It should also be noted that while Menkes disease (insufficient copper) and Wilson disease (excess copper) both cause neurodegeneration, the specific appearance of the neurodegeneration is very different. Specifically, Wilson disease mostly affects the brain after it has developed. "Wilson's neurodegeneration encompasses the striatum and pallidum and to a minor degree cerebral cortex, brainstem, and dentate nucleus" [3]. There is also "a more pronounced glial pathology and signs of inflammation in Wilson disease" [3]. Wilson disease also produces distended mitochondria, though specifically in the liver and neurons, which possibly explains why those are the two organs most impacted by the disease. These distended mitochondria are likely caused by copper overload leading to the perikaryon having engorged organelles [3]. While it has long been understood that copper can act as both a noxious agent or an enzymatic cofactor, it is also being discovered that it can also "operate as an allosteric modulator of signal transduction or a second messenger capable of integrating the metabolic activity of the Golgi complex, mitochondria, and plasma membrane metal transport" [3]. These aspects may have unexplored impacts on a range of insufficiently understood neurological disorders [3].

Conclusion

Copper has been shown in the past to have a negative impact on the viability of multiple different types of viruses [5, 9, 10], both directly and indirectly. "Copper can boost the host's immune system response against pathogens, exhibiting strong antibacterial, antifungal, antiviral and antiinflammatory effects" [13]. Ongoing research has "established that the complex, integrated immune system needs multiple specific micronutrients, including vitamins A, D, C, E, B6, and B12, folate, zinc, iron, copper, and selenium, which play vital, often synergistic roles at every stage of the immune response" [1]. It is very important to note that "the European countries worst hit by the pandemic show population% with suboptimal intake of vitamins and minerals that are important to the immune system" [7]. This combination of immune support with active antagonism to viral particles suggests that copper may help individuals who have been exposed to COVID-19 fight off infection.

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