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Is copper beneficial for COVID-19 patients?

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ABSTRACT

Copper (Cu) is an essential micronutrient for both pathogens and the hosts during viral infection. Cu is involved in the functions of critical immune cells such as T helper cells, B cells, neutrophils natural killer (NK) cells, and macrophages. These blood cells are involved in the killing of infectious microbes, in cell-mediated immunity and the production of specific antibodies against the pathogens. Cu-deficient humans show an exceptional susceptibility to infections due to the decreased number and function of these blood cells. Besides, Cu can kill several infectious viruses such as bronchitis virus, poliovirus, human immunodeficiency virus type 1(HIV-1), other enveloped or nonenveloped, single- or double-stranded DNA and RNA viruses. Moreover, Cu has the potent capacity of contact killing of several viruses, including SARS-CoV-2. Since the current outbreak of the COVID-19 continues to develop, and there is no vaccine or drugs are currently available, the critical option is now to make the immune system competent to fight against the SARS-CoV-2. Based on available data, we hypothesize that enrichment of plasma copper levels will boost both the innate and adaptive immunity in people. Moreover, owing to its potent antiviral activities, Cu may also act as a preventive and therapeutic regime against COVID-19.

Introduction

Copper (Cu) is an essential trace element for humans [1]. Dietary Cu is absorbed in the small intestine and is rapidly appeared in the circulation. In blood, Cu is distributed into a plasma pool associated with larger proteins, an exchangeable fraction of low molecular weight copper complexes, and a red cell pool that is partly nonexchangeable. Cu plays an important role in the function and maintenance of the human immune system. Cu is involved in the functions of T helper cells, B cells, neutrophils, natural killer cells and macrophages. These cells are involved in the killing of infectious microbes, cell-mediated immunity and production of specific antibodies. Cu deficiency symptoms in human include deficiencies in white blood cells, bone and connective tissue abnormalities, and immune reactions [2]. Adverse effects of insufficient Cu on immune function appear most pronounced in infants and older people. Infants with genetic disorders that result in severe Cu deficiency suffer from frequent and severe infections [2,3]. During infection, macrophages can attack invading microbes with high Cu load. Cu is also elevated at sites of lung infection during infection with a wide array of pathogens [4]. Cu deficiency and its excess levels can result in abnormal cellular function or damages that given its central role in host-pathogen interaction. The molecular interplay between the virus and the cellular machinery manages Cu^{2+} flux [5]. Subtle alterations of Cu homeostasis can occur in infectious diseases and results in toxic Cu accumulation to eliminate pathogen [6]. Dietary Cu deficiency affects both innate and adaptive immunity [7]. In fact, Cu-deficient humans show an exceptional susceptibility to infections. Besides, Cu can kill several infectious viruses such as bronchitis virus, poliovirus, human immunodeficiency virus type 1(HIV-1), other enveloped or nonenveloped, single- or double-stranded DNA and RNA viruses [2,8]. Cu-induced viral killing may be mediated via ROS [9], and in this regard, Cu^{+} and hydrogen peroxide play the essential roles [10]. The contact killing of bacteria, yeasts, and viruses on metallic Cu surfaces is well studied [11]. Cu supplementation was shown to restore the secretion and activity of IL-2 in Cu-deficient animals via increased synthesis of IL-2, which is crucial for T helper cell proliferation and NK cell cytotoxicity [12,13]. It is still not clear how copper deficiency alters´protein expression to produce observed pathologies. Transcript profiling, proteomic analysis, and metabolite profiling, in both data-driven and targeted formats, promise to provide more mechanistic details in animal models that can be tested in human pathology. Cu also normalized impaired immunological functions by modulating neutrophil activity,

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blastogenic response to T helper cell mitogens, the balance between Th1 and Th2 cells [14].

Antiviral activity of Cu

Cu has the potent capacity to neutralize infectious viruses such as bronchitis virus, poliovirus, human immunodeficiency virus type 1(HIV-1), and other enveloped or nonenveloped single- or double-stranded DNA and RNA viruses [15]. Cu can disrupt the lytic cycle of the Coccolithovirus, EhV86 with the increase in production of ROS [15]. Cu^{2+} ions can inactivate five enveloped or nonenveloped, single- or double-stranded DNA or RNA viruses. The virucidal effect of this Cu is enhanced by the addition of peroxide as the mixtures of Cu^{2+} ions and peroxide are more efficient than glutaraldehyde in activating Junin and herpes simplex viruses [15]. Copper exposure to human coronavirus 229E destroyed the viral genomes and irreversibly affected virus morphology, including disintegration of envelope and dispersal of surface spikes [16]. Cupric (II) chloride dihydrate showed the inhibitory effect on the replication of dengue virus, DENV-2 in a cell culture study [17]. Cu-chelating agent (ATN-224) can reduce plasma-mediated inhibition of herpes simplex virus-derived oncolytic viruses (oHSV) indicating the importance of Cu^{2+} ions in this process. Thujaplicin-Cu chelates inhibit influenza virus-induced apoptosis of MDCK cells and also inhibit the virus replication and release from the infected cells [18]. Cu^{2+} ions inactivate herpes simplex virus by oxidatively damaging its genome [15]. Cu surfaces can significantly reduce the number of infectious influenza A virus particles. Cu ions can damage the viral genomic DNA by binding and cross-linking between and within strands of the genome [19]. Replication of influenza A virus was inhibited by Cu by damaging the negative-sense RNA genome [19]. The contact killing of microbes by Cu is mediated by the degradation of genomic and plasmid DNA of microbes [20]. Human coronavirus was rapidly inactivated on a range of Cu alloys Cu/Zn brasses were very effective at lower Cu concentration that Cu(I) and Cu(II) moieties were responsible for the inactivation which was enhanced by ROS generation on alloy surfaces [21]. Novel coronavirus (SARS-CoV-2), responsible for current COVID-19 pandemic is very sensitive to the copper surface [22]. In a cell-based study, Cu^{2+} was shown to block papain-like protease-2, a protein that SARS-CoV-1 requires for replication [23,24]. Oxidized Cu oxide (CuO) nanoparticles (CuONPs) are widely used as catalysts so that the ability of CuONPs to reduce virus application is enhanced [25]. Nanosized Cu(I) iodide particles also show inactivation activity against H1N1 influenza virus. Gold/Cu Sulfide core-shell nanoparticles (Au/CuS NPs) exhibit variable virucidal efficacy against human norovirus (HuNoV) via inactivation of viral capsid protein [25].

Hypothesis and argument

The current outbreak of the novel coronavirus SARS-CoV-2 (coronavirus disease 2019, COVID-19), infected around the world. There are nearly 1.9 million confirmed cases of coronavirus in 185 countries, and at least 120,000 people have died, as of April 14, 2020. Coronaviruses are enveloped, positive single-stranded large RNA viruses that infect humans, but also a wide range of animals. Coronaviruses were first described in 1966 by Tyrell and Bynoe, who cultivated the viruses from patients with common colds [26]. At present, no vaccines exist that protect people against infections by SARS-CoV-2, which causes COVID-19. As COVID-19 continues to wreak havoc and many labs around the world are engaged in clinical trials involving several drugs those affecting viral pathways such as remdesivir, arbidol hydrochloride combined with interferon atomization, ASC09F plus oseltamivir, ritonavir plus oseltamivir, lopinavir plus ritonavir, mesenchymal stem cell treatment, darunavir plus cobicistat, hydroxychloroquine, and methylprednisolone. The world is now desperate to find ways to slow the spread of the SARS-CoV-2 and to find effective treatments. People with weakened immune systems are always at an increased risk of infectious diseases, and COVID-19 is no exception. Several reports demonstrated that Cu deficiency weakens the human immune response. Moreover, Cu deficiency can over-activate neutrophils and cause them to build up in the liver, which contributes to inflammation. Most people get enough Cu from diet, supplements, and water. Cu deficiency is rare and usually only occurs in seriously ill people receiving intravenous (parenteral) nutrition that lacks Cu [27,28]. The under-detection of Cu deficiency could be due to limitations of screening using serum or urine samples. Cu deficiency is not usually about a lack of Cu, but an imbalance of Cu and other minerals in the diet that need to be supplemented with minerals and failure to do so may inhibit their potential to produce Cu that can lead to susceptibility towards infection. While severe Cu deficiency has adverse effects on immune function, the effects of Cu insufficiency in humans are not yet well known. In humans, the Cu status, tested by plasma Cu or ceruloplasmin or cuproenzymes, is strictly dependent by individual dietary habits and health status, and ultimately plasma ceruloplasmin levels. Serum level of Cu level is higher in pregnant women than that of non-pregnant women. In Wenzhou, China a study of 71 patients showed that those infected with COVID-19 have significantly lower total cholesterol levels in serum compared to healthy controls [29]; however, it is not known whether they had lowered Cu levels too. Several studies have shown that lower total cholesterol level may be related in part due to lower Cu level in adults [21,30,31]. Disruption of lipid rafts by cholesterol depletion caused an enhancement of virus particles released from infected cells and a decrease in the infectivity of virus particles [32]. Plasma Cu may affect all these above processes. Cu oxide nanoparticles and Cu^{2+} ions are involved in the inhibition of viral entry and replication, and degradation of mRNA and capsid proteins that are involved in the viral life cycle. Cu deficiency is not always about a lack of Cu but also could be the result of an imbalance of Cu and other minerals in the diet that may often occur in an older population. In older people, Cu deficiency can also result from malnutrition, malabsorption, or excessive zinc intake and can be acquired or inherited [28]. Copper deficiency could lead a decreased number of circulatory blood cells with a greater susceptibility towards infection in older people In a study of 11 men on a low-Cu diet (0.66 mg Cu/day for 24 days and 0.38 mg/day for another 40 days) showed a decreased proliferation response of their white blood cells when presented with an immune challenge in cell culture [33]. Recent mechanistic studies support a role for Cu in the innate immune response against infections [34]. In the condition of specific intestinal malabsorption (such as celiac disease, bowel syndrome, long-term parenteral nutrition) or bone abnormalities or in well genetically determined disease (Menkes' disease), Cu deficiency is severe with dysfunctions on immune response, antioxidant activity and bone metabolism [35]. Altered plasma and tissue levels of Cu in acute or chronic inflammation reflect the changes in the metabolism of Cu [36,37]. We hypothesize that copper supplementation can help fight COVID19, especially in older people where marginal or severe deficiency of Cu is a strong possibility. Because Cu and zinc are competitively absorbed from the jejunum via metallothionein, high doses of zinc (> 150 mg/day) can result in Cu deficiency in healthy individuals. It is possible that people are may be at risk of severe SARS-CoV-2 infection, who are also taking Zn supplement regularly. While high copper levels can be poisonous, sites which are Cu limited can result in stress responses by pathogens that warrants that the Cu levels must be maintained optimally. At present, we do not have enough data or knowledge concerning the effect of therapeutic supplementation of Cu regarding the susceptibility and outcome of COVID-19. Dietary or therapeutic Cu supplementations might affect host immune function and metabolism of other micronutrients and prevent the severity of the viral infection. Therefore, supplementation of Cu and correction of mineral deficits may be beneficial for COVID-19 patients. Such knowledge is essential to our understanding of how alterations in Cu availability affect host-pathogen interactions and the course of infections, and it will likewise also results in the identification of new

therapeutic strategies targeting host or microbial metal homeostasis during infection. We thus urgently need more preclinical studies and multi-centre prospective clinical trials in this area. Compilation of data on toxicity due to copper excess and deficiency yielded a generalized linear model that was used to estimate adverse responses depending on copper dose or severity of copper limitation, as well as the duration of copper misbalance [38]. This model indicates that for humans, the optimal intake level for Cu is 2.6 mg/day. The current United States Recommended Daily Intake is only 0.9 mg (USA Food and Nutrition Board), whereas dietary study indicated that even 1.03 mg of Cu/day might be insufficient for adult men [39]. The results of the third National Health and Nutrition Examination Survey (NHANES III, 2003) in the USA showed that the mean daily intake of Cu, depending on age, was 1.54–1.7 mg/day for men and 1.13–1.18 mg/day for women. These results imply that a large portion of the population may have insufficient dietary copper intake and mild copper deficiency. We argue that Cu supplementation may have a protection of people from COVID-19.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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