European Journal of Biology and Medical Science Research
Vol.8, No.4, pp.1-7, June 2020
Published by ***ECRTD- UK***
Print ISSN: ISSN 2053-406X, Online ISSN: ISSN 2053-4078

ZINC AND COVID-19: NOVEL WAYS TO MAINTAIN OPTIMAL ZINC BALANCE

Yuzo Nishida
Disease Absorption System Technologies Co., Ltd (DASTec). 920-0226 Kanazawa-city, Ishikawa-Pref. Japan. E-mail: nsd-2210@kanazawa-med.ac.jp

ABSTRACT: *The earlier studies have shown that zinc deficiency can hinder host-defense systems to increase the susceptibility to various viral and bacterial infections, and thus in view of the global COVID-19 pandemic, potential protective effect of zinc is of particular interest. As it has become clear that zinc deficiency is induced by the non-transferrin-bound iron (NTBI) based on the our works, the use of our non-toxic iron chelators can be recommended as the supportive treatment in therapy of COVID-19 infection, because our iron chelators may prevent the zinc deficiency by inhibiting the formation of iron deposition containing much iron and zinc ions through removing or controlling the iron(III) ions in NTBI.*

Keywords: Zinc, COVID-19, NTBI , Iron Deposition, Anti-oxidant Function

INTRODUCTION

Zinc is an important dietary trace mineral that acts in the activation and inactivation of over 300 enzymes and coenzymes that are involved in the vital cellular functions, including energy metabolism, DNA synthesis, RNA transcription, etc. (Field et al. 2002; Overbeck et al. 2008). At the same time the most critical role of zinc is demonstrated for the immune system. Under zinc deficiency condition, organisms are more susceptible to toxin-producing bacteria or enteroviral pathogens that activate guanylate and adenylate cyclases, and earlier studies have shown that zinc deficiency can hinder host-defense systems to increase the susceptibility to various viral and bacterial infections (Prasad, 2007; Fraker et al. 2000). Preexisting chronic metabolic diseases including diabetes, cardiovascular disease, and obesity are considered as risk factors for increased COVID-19 susceptibility and mortality (Zhang & Liu, 2020).

Of clinical importance, severe acute respiratory syndrome (SARS) coronavirus replication has shown to be inhibited by zinc (Velthuis et al., 2010). Zinc compound has also shown to reduce the in vitro replication potential of the influenza virus (Velthuis et al. 2010), and antiviral effects of zinc are also shown in the hepatitis C virus (HCV) (Uchida et al. 2002), where zinc salts reduced the HCV replication. More importantly, zinc supplementation in HCV-infected patients reduced hepatitis and enhanced the response to antiviral treatment (Matsumura et al.

2012; Matsuoka et al. 2009; Murakami et al. 2007). Zinc is considered as the supportive treatment in therapy of COVID-19 infection due to its immune modulatory effect as well as direct antiviral effect, however the existing data will be only mechanically discussed, since direct data on anti-COVID-19 effects of zinc are absent to date. In view of the global COVID-19 pandemic, potential protective effect of zinc is of particular interest.

NTBI AND IRON DEPOSITION

Plasma iron is normally bound to the iron transport protein transferrin (Dresow, Peterson, Fischer, & Nielsen, 2008). When excess chelates (amino acids derivatives, small peptides or citrate, etc.) are present in the plasma, the water-insoluble hemosiderin which contains polymeric iron(III) ions with oxo-bridges may dissolve with forming the water-soluble iron(III) chelates with amino-acids or citrates. These iron ions not associated with transferrin is generally termed as non-transferrin-bound iron (NTBI). NTBI is detected in the plasma of patients with hemochromatosis and several neurodegenerative disorders, such as Alzheimer's and Parkinson's diseases, multiple sclerosis, and aceruplasminemia (Gaeta & Hider, 2005; Evans, et al. 2008; Yoshida et al., 2000; Stankievicz et al., 2007; Roberts et al. 2012), and is present at concentration up to 10 μM. It should be noted here that the water-soluble NTBI has been thought to play a crucial role in iron induced cell damage with resultant peroxidation of cell membrane lipids and other biomolecules, and such oxidative damage is implicated as an important contributor in the pathogenesis of cancer, cardiovascular disease, aging and neurodegenerative diseases.(Gaeta & Hider, 2005; Nishida, 2004; 2012b, 2012c)

In addition to these water-soluble NTBI, it is well known that iron deposition, which is water-insoluble NTBI, is frequently observed for the patients with hemochromatosis and several neurodegenerative disorders, such as Alzheimer's and Parkinson's diseases, multiple sclerosis, etc. (Yoshida et al., 2000; Stankievicz et al., 2007; Roberts et al. 2012). Despite numerous studies over the last 30 years since plasma NTBI was first postulated to exist, it is still poorly characterized. The inability thus far to characterize NTBI most likely reflects both its heterogeneous nature and the likelihood that the different forms will exist and vary with the concentration of the chelates such as amino-acids, peptides, and citrate, etc. Very recently, Nishida have proposed that the iron deposition should be aggregation of the di-μ-oxo bridged dimeric Fe(III) complex based on the several observed facts (Nishida, 2012a, 2012b, 2012c).

IRON DEPOSITION BY ZINC TO INDUCE ZINC DEFICIENCY

In our previous paper, we have showed that iron deposition occurs readily when zinc(II)

chloride solution is added to the solution containing Aβ (1-40) and iron(III) compounds with tetradentate ligand (nta) or (edda) (Okawamukai, Sutoh, & Nishida,2006), and also by adding the iron(III) compound solution to the mixed solution of Zn(II) chloride and Aβ (1-40) containing the white Zn(II)/Aβ (1-40) precipitation; here Aβ represents amyloid β–protein. Similar iron deposition has occurred when another protein, such as albumin, etc was used instead of Aβ (1-40), and Nishida have proposed the formation mechanism of iron deposition (Nishida, 2012a, 2012b).

In addition to the above, we also found that zinc(II) ion leads to the iron deposition formation (see Figure 1) when the binuclear iron(III) complex with an alkoxo-bridge $[Fe_2(HPTP)Cl_4]^+$ ion was added to the solution containing Aβ (1-40) and zinc(II), where H(HPTP) represents N,N,N',N'-tetrakis(2-pyridylmethyl)-1,3-diamino-2-propanol (Nishino et al. 1999). It should be noted that much iron (III) and zinc (II) ions are included in the brown deposition in Figure 1.

Figure 1. **I.** Zinc (II) chloride (10 μl, 1 M) was added to the Aβ (1-40) solution (100 μl, 0.25mg/ mL). **II.** $Fe_2(HPTP)Cl_4ClO_4$ solution (50 μl, 2 mg/mL) was added to the solution **I.** Brown precipitates occurred immediately upon the addition of $Fe_2(HPTP)Cl_4ClO_4$ solution.

Since the total zinc(II) concentration is relatively reduced compared with that of normal cases and massive iron deposition are observed in the brain and on several organs such as kidney or spleen of the patients of aceruplasminemia (Yoshida et al., 2000) and other neurodegenerative disorders such as Alzheimer's and Parkinson's diseases etc. (Grabrucker et al., 2011), it seems reasonable to assume that zinc(II) ions play an important role on the formation of the iron deposition in these patients. Since the formation of the iron deposition means the deletion of toxic NTBI from the plasma, we can consider that zinc (II) ions act as an antioxidant in the

patients of several neurodegenerative disorders. Thus, the amyloid deposition which frequently observed for the Alzheimer's patients, may be due to one of the anti-oxidative function by zinc(II) ion (Okawamukai et al. 2006; Nishida 2012a, 2012b, 2012c). These are showing that zinc(II) ion supplementation will give useful therapeutic methods to prevent the many neurological disorders (Grabrucker et al. 2011), and also demonstrate that the presence of NTBI easily induce the zinc deficiency state, which is consistent with the observed facts (Yoshida et al., 2000; Stankievicz et al., 2007; Roberts et al. 2012).

NEW CHELATING AGENTS TO PREVENT ZINC DEFICIENCY

Very recently we have prepared the so-called *super-polyphenols* which contain more than 100 molecules of catechol derivative in one polymeric compound, chitosan (Nishida, 2015) (see Figure 2). We found that water-insoluble super-polyphenols can eliminate NTBI effectively *in vitro study*, as exemplified in Figure 3. Our super-polyphenols in Figure 2 are characterized in the following four points, 1) the super-polyphenols are water-insoluble, 2) these are not metabolized in the human body due to its insolubility in water and its polymeric structure (MW~90,000), 3) their iron (III) chelates are also water-insoluble, and 4) they do not interact with the iron ions in the holo-transferrin. The property 4) clearly indicates that our super-polyphenols can discriminate the necessary iron ion and unnecessary iron ion (NTBI) in the human body, and can remove only the NTBI from the body.

Over the past decade, research with curcumin has increased significantly (Belkacemi et al, 2011). In vitro and in vivo studies have demonstrated that curcumin could target pathways involved in the pathophysiology of Alzheimer's disease (AD). These findings suggest that curcumin might be a promising compound for the development of AD therapy, but its insolubility in water and poor bioavailability have limited clinical trials and its therapeutic applications. We have found that the water-insoluble super-polyphenol containing vanillin derivative (FC-Vani4 in Figure 2) shows high ability to catch NTBI through chelation, implying that the antioxidant, anti- inflammatory, anti-proliferative properties of curcumin should be due to its ability to excrete NTBI.

Thus it seems quite likely that water-soluble or water-insoluble super-polyphenols developed by us (Nishida, 2015; 2020) can prevent zinc deficiency and also prevent several neurological disorders, such as dementia, Alzheimer's and Parkinson's diseases, and COVID-19. The water-insoluble compounds in the Fig. 2 may be artificial lignin model compounds (Nishida, 2015); the lignins are contained in the roots, leaves, and stems of various plants and vegetables, and

generally insoluble in water. We observed that the roots, leaves, and stems of various plants and vegetables can catch the NTBI from the solution including Fe(III)-nta, similar to those illustrated in Figure 3. These are suggesting that Japanese foods can prevent the zinc deficiency, because Japanese foods contain many lignin derivatives of plants and vegetables, and this should be one of the main origin for "Japan Paradox".

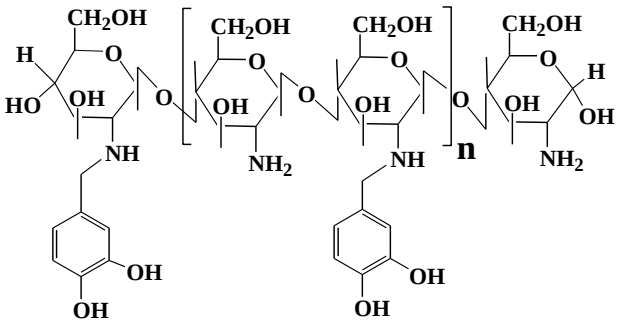

Figure 2. Chemical structure of super-polyphenol, FC-Cate2. The –OH group of the benzene ring can be replaced by –COOH (FC-Carb2) or $–OCH_3$ (FC-Vani4) group.

Figure 3. Super-polyphenols can catch the iron(III) ions of the Fe(III)-nta solution, removing the iron(III) ion from the solution
Left: solution of Fe(III)-(nta) chelate (Nishida, 2012b)
Center: FC-Carb2 (solid) was added to the Fe(III)-(nta) solution
Right: FC-Cate2 (solid) was added to the Fe(III)-(nta) solution

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