PIONEER
MEDICAL JOURNAL

Vol. 2 No. 1 Jan. - June., 2022

ERRATUM:
This article was inadvertently republished under Volume 2, No. 1 (July–June 2022)
following a redesign and restructuring of the journal website.
The correct bibliographic designation for this article is Volume 8, No. 1 (January–June 2023),
under which it was originally published.
This correction affects only the volume, issue, and publication-period metadata.
The article content, DOI, authorship, pagination, and publication date remain unchanged.

www.pioneermedicaljournal.com
ISSN: 2354 - 1954

Official Publication of The Medical and Dental Consultants' Association of Nigeria ***(MDCAN)***
FMC, Umuahia Chapter.

Editor In-Chief
DR. CHIMEZIE GODSWILL OKWUONU

PIONEER MEDICAL JOURNAL

FMC, UMUAHIA

Clinical Review

A Review of Zinc; An Essential Antioxidant Trace Element in the Elderly

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Abstract

Zinc is an important antioxidant trace element absorbed through metallothioneins in the small intestine. With a total body zinc mass of 2-4g in an adult, and seen in all classes of enzymes, zinc is involved in many metabolic functions such as protein synthesis, DNA synthesis, cellular growth, innate and acquired immunity as well as several antioxidant detoxification. Uncontrolled oxidative stress and subsequent inflammation is an initiator of Alzheimer's dementia. Zinc and other antioxidant supplementation is the main treatment of age-related macular degeneration. Oxidative stress plays a major role in depression. Serum zinc correlates with mental efficiency in the elderly, while low serum levels was demonstrated in elderly persons with major depressive disorder. Zinc administration has positive metabolic effects in chronic liver disease such as attenuation of inflammation and reduction of hepatic steatosis, improvement of insulin resistance and attenuation of hepatic encephalopathy. Maintaining adequate circulating zinc may reduce free radical damage to the DNA. Free radical damage is one of the theories of cancer pathogenesis. Low serum zinc levels have been reported in cervical cancer, liver cancer, oral cancer, pancreatic cancer and prostate cancer. Lower levels of zinc correlated with more severe and advanced prostate cancer.

The elderly person is prone to malignancies and other chronic diseases. The aim of this review is to refresh the clinician and the academic on zinc metabolism and the metabolic benefits of this antioxidant trace element in minimizing chronic diseases and the need for adequate micromineral nutrition in the elderly.

Keywords : trace element, zinc, elderly, micromineral nutrition

Running title:Okwara EC - Zinc, an essential antioxidant in the elderly

Background

Poor nutritional intake and chronic diseases common in the elderly such as depression, Alzheimer's dementia, carcinomas,

ischaemic heart disease and cardiac failure of any origin are commonly associated with vitamin and mineral derangements` including trace elements, particularly antioxidant trace elements[1-4]. Although cause-and-effect relationships for these diseases and antioxidant trace elements are still being debated[5,6], the benefits of these trace minerals in minimizing cell ageing and modifying the progress of diseases are well known[7-9]. Ratios of one trace element to another (such as serum copper to serum zinc ratio or iron to zinc ratio) and signature patterns of decrease and increase in serum levels of antioxidant trace elements may offer prognostic tools in some chronic diseases common in the elderly[1,2,3,10]. Such prognostic tool will complement existing screening and diagnostic procedures for disease risk stratification and monitoring.

Trace elements are chemical micronutrients which are required in minute quantity but play pivotal role in maintaining the effectiveness of various physiological and metabolic processes in living tissues[11]. Their daily requirement is below 100mg[11]. Antioxidant trace elements are trace metals that play roles in scavenging reactive oxygen and nitrogen species, also known as free radicals, thereby reducing oxidative stress[11]. Although free radicals have some beneficial cellular effects such as the killing of bacteria, any imbalance that promotes their excessive formation has deleterious consequences on the cell. Mitochondria are the main source of reactive oxygen species; as by-product of the electron transport chain. Antioxidant trace elements serve as constituents of free radical detoxification metalloenzymes and as enzyme activators. Excessive generation of free radicals implies oxidative stress and is implicated in ageing and several chronic diseases, either as a cause of or facilitator of disease progress. Antioxidants functions to prevent excessive accumulation of free radicals in living systems. Zinc, selenium, copper, manganese and iron are trace elements with antioxidant characteristics[12-15]. Iron is the most abundant trace element but is excluded in the WHO classification of trace elements[11,16]. Serum levels of some trace elements may vary across populations in different geographic areas and as well as across different age groups in the same geographic area[8,17]

The Trace Elements

The human body requires some mineral nutrients in small quantities for normal body function. The shortage or excess of these minerals could lead to severe malfunctioning of the body and in some extremes even death. Trace elements refer to those elements existing in natural or perturbed environments in small amounts but are pivotal to healthy living while excess bioavailability has toxic effects to the body[15]. They are also described as chemical micronutrients which are needed in minute quantities if the integrity of the body's physiologic and metabolic systems is to be maintained[15]. Their serum levels are affected by several disease processes and in turn they may modify the progress of diseases process[8,18,19]. Food is the chief source of these micronutrients, other sources being water and by inhalation. Nutritional deficiencies are common in the elderly and deficient levels of micro-minerals have been severally reported in the elderly[17,19].

Classification of Trace Elements

Not much effort has been made to classify trace elements.

World Health Organization (WHO) Classification

In 1973 the WHO divided 19 trace elements into 3 groups[15,16]

1. Essential trace elements comprising zinc (Zn), copper (Cu), selenium (Se), chromium (Cr), cobalt (Co), iodine (I), manganese (Mn) and molybdenum (Mo).
2. Probably essential trace elements comprising cadmium (Cd), nickel (Ni), silicon (Si), tin (Sn), vanadium (V) and aluminium (Al).
3. Potentially toxic elements comprising gold (Au), mercury (Hg), Arsenic (As), lithium (Li), and lead (Pb).

Frieden's Classification of Trace elements

In 1981 Frieden classified trace elements based on the quantities they occur in living tissues into 3 groups much similar to the WHO classification[15,20-22].

1. Essential trace elements: boron, cobalt, iodine, iron, manganese, molybdenum and zinc.
2. Probably essential trace elements: chromium, fluorine, nickel, selenium and vanadium.
3. Physically promotive trace elements: bromine, lithium, silicon, tin and titanium

Note that selenium is classified as essential trace element by the WHO classification but probably essential trace element by the Frieden's classification.

Antioxidant Trace Elements

Antioxidant trace elements are those essential trace elements that participate in the detoxification of free radicals thereby reducing oxidative stress. They take part in scavenging excessive reactive oxygen and nitrogen species hence minimizing the cellular damaging effects of these reactive species. Antioxidants capture and inhibit the formation of free radicals and also chelate metal ions that catalyze the free radical chain reactions[12]. The antioxidant trace elements detoxify free radicals mainly by being constituents of metalloprotein enzymes that detoxify reactive species[12,23]. These essential trace elements include zinc, selenium, copper, manganese and iron.

Selenium is a constituent of glutathione and many selenoproteins that scavenge free radicals. It is also a component of the antioxidant enzyme, glutathione peroxidase[,24-27]. Zinc, copper and manganese are components of the group of superoxide dismutase enzymes, copper-zinc superoxide dismutase (Cu/ZnSOD) and manganese superoxide dismutase (MnSOD), that catalyze superoxide ion (a free radical) dismutation into hydrogen peroxide and water[12]. Iron is a component of the enzyme catalase that breaks down the hydrogen peroxide into water and oxygen thereby reducing oxidative stress[12]. Hydrogen peroxide can also be broken down to the same products by glutathione peroxidase. Copper, iron and zinc may also act as pro-oxidants in some situations[3,28].

Zinc

Zinc is the second most abundant trace element in the body with a total amount of 2 - 4g in an adult and is the metal element that is seen in all classes of enzymes[15]. The major source of zinc to man is the animal components of food. Zinc is involved in many metabolic functions including protein synthesis, DNA synthesis, cellular growth, innate and acquired immunity and antioxidant detoxification[23]. Zinc ions show effective antimicrobial properties at low concentrations, thus can be used as topical antimicrobial and anti-inflammatory agents[15]. The average daily requirement of zinc is 15 – 20 mg in an adult[22].

Zinc Metabolism

Zinc is absorbed through metallothioneins (MTs) in the small intestine[15]. Metallothionein is a family of cysteine-rich (30% of components are cysteine residues) low molecular weight proteins localized in the membranes of the Golgi apparatus that has the physiologic capacity to bind to zinc, copper, selenium and the heavy metals through the thiol group of their cysteine residues[29].Excess zinc in the diet can, therefore, impair copper and selenium absorption through shared sites in MTs[15]. After absorption in the small intestine it is transported in the blood with 60% bound to albumin and 10% bound to transferrin[15]. Transferrin is the transport protein to iron, therefore, excess of either trace element will hinder the absorption of the other. Zinc is stored in the liver, prostate, parts of the eye, brain, bones and kidneys[22]. Zinc is excreted through the pancreas, intestine, sweat glands and proximal tubules of the kidneys[22].

Zinc impedes the formation of Fe-oxygen-enoic acid complex which initiates lipid peroxidation and can as well impede the propagation step of this free radical production pathway[28]. This action of zinc protects macromolecules and biological membranes from oxidative and peroxidative damage. Pharmacological administration of zinc showed antioxidant benefits in the alimentary tract in alcohol intoxication, whole body irradiation and isoproterenol oxidative cardiac damage[28]. Isoproterenol, also called isoprenaline is a non-selective β-adrenergic agonist and an analog of adrenaline used in treatment of brardycardia and heart block both of which are common in the elderly.

Zinc also plays antioxidant roles by being a component of Cu/Zn SOD (as well as by Zn^{2+} induction of this enzyme), glutathione S-transferase, haemoxygenase-1 and nuclear factor erythroid 2-related factor 2 (Nrf2), all of which are antioxidant enzymes[28].

Adequate amounts of zinc in diet or supplement is considered essential in slowing down the ageing process and in turn improve immune functions, achieve adequate response to stress, reduce age-related neurodegenerative disorders and improve cognitive functions[28].

Zinc and Neurodegenerative Diseases

One of the challenges of ageing and modern medicine is the prevention and treatment of Alzheimer's dementia (AD) being the most dreaded form of dementia. Dementia, including AD is projected to rise globally from 31.5 million in 2015 to 46.8 million in 2050[4]. Uncontrolled oxidative stress and subsequent inflammation are part of the initiators of AD with heavy metals playing active parts in amyloid deposition[4]. Besides this, heavy metals themselves such as arsenic and cadmium can strongly interact with proteins and DNA and cause site-specific damage that lead to the conformational change in proteins and DNA as well as the excessive production of free radicals[28]. A distinctive pattern of serum zinc, selenium, manganese and iron during the progression of AD has been reported[4]. This could lead to pre-clinical staging of AD more than a decade before onset of the clinical disease. It could be crucial in the management of AD.

Parkinson disease (PD) is a progressive neurodegenerative disorder associated with motor symptoms such as tremor, rigidity, slowness of movement and postural instability[30]. Its incidence rises steeply with age and the life time risk of developing the disease is 1.5%[30]. The levels of zinc in plasma and serum were reported to be reduced in PD in a meta-analytical study[30].

Zinc was reported to be deficient in 71% of elderly Yoruba people in a slum of Ibadan,

Nigeria and 28% of elderly in a nursing home in Poland[19,31].

Zinc Depletion and Age-related Macular Degeneration

Age-related macular degeneration (AMD) is an acquired disease of the macula characterized by progressive visual impairment due to its late-onset neurodegeneration of the photoreceptor-retinal pigment epithelial complex[32]. The disease could be the atrophic AMD or wet AMD. It causes central visual loss in 10% of people older than 65 years and 25% of persons older than 75 years in developed countries[32]. Its aetiology is still unclear but established risk includes 60 years or more of age, smoking, tobacco intake and family positive history of AMD. Patients with AMD with high levels of complement catabolism at baseline demonstrated a steep decline in complement catabolism after 3 months of oral zinc supplementation[18]. Those with low level complement catabolism at baseline showed less decline in complement catabolism after zinc supplementation. Zinc and other antioxidant supplementation along with close observation is the main treatment of atrophic AMD[32].

Zinc Depletion and Depression

Depression affects millions of people globally and is a major cause of disability worldwide. Recent studies indicate that oxidative stress plays key roles in the pathogenesis of depression[33]. The brain appear to be more prone to free radical damage due to high content of unsaturated fatty acids, high oxygen consumption, high contents of key requirements for lipid peroxidation and low content of antioxidant defense systems[33]. Serum total antioxidant capacity (TAC) was reported lower in patients with depression while free radicals and products of oxidative damage were higher in these patients [33]. In a group of elderly people in a nursing home in Poland serum zinc level correlated with mental efficiency and was statistically significantly higher in older people with normal cognitive function and without depression than in patients with memory impairment showing depressive symptoms[31].

Patients with major depressive disorder (MDD) demonstrated significantly lower levels of serum zinc during episodes of depression when compared with healthy volunteers [34]. Contrary to this finding, patients achieving remission showed no statistically significant difference in zinc levels when compared with healthy volunteers[34]. This study suggested that serum zinc may be a biomarker of MDD.

Women suffer depression two to three times more than men and the menopausal period appear to be extremely conducive for depression[35]. The lowest concentration of zinc was reported in women with severe depression and highest in those with mild or no depression[35].

Zinc Status in Cardio-metabolic Diseases

Zinc homeostasis is mainly regulated in the liver, thus chronic liver damage will lead to deficiency. In patients with chronic hepatitis, zinc deficiency in turn propagates oxidative stress that will lead to a number of metabolic problems such as insulin resistance, hepatic steatosis and further damage to the liver. Iron overload, due to shared absorption site in MT and hepatic encephalopathy is also a consequence of zinc deficiency in chronic hepatitis[36]. Zinc administration has favourable effects on the metabolic problems seen in chronic liver disease such as attenuation of hepatic inflammation, improvement of insulin resistance, attenuation of hepatic steatosis,

improvement of hepatic encephalopathy, etc[36].

Reduced levels of zinc were reported in patients with ischaemic heart diseases (IHD) as well as in patients with cardiac failure of any origin[2,3]. Findings suggest that serum Cu/Zn ratio and Fe/Zn ratio may provide additional index for prognostication of IHD.

Zinc Depletion and Cancers

Free radical damage to the DNA is one of the theories of cancer pathogenesis. Maintaining an adequate level of circulating zinc may have important role in prevention of the development of liver cancer[37]. Low levels of zinc were reported in patients with cervical cancer, liver cancer, oral cancer, pancreatic cancer and prostate cancer[1,6,37-39]. A lower serum zinc level was associated with more severe and advanced prostate cancer disease[39]. Copper / zinc ratio may have role in disease prognosis and monitoring.

Conclusion

Zinc is a very essential antioxidant trace element with numerous beneficial roles, especially in the elderly. Adequate amounts of zinc in diet or dietary supplement is considered essential in slowing down the ageing process as well as improving immune functions, achieve adequate response to stress, reduce age-related neurodegenerative disorders and improve cognitive functions.

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