ORIGINAL RESEARCH PAPER | Zoology | Volume : 6 | Issue : 10 | October 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

Erythrocyte Zinc, Free Radicals and Antioxidants

KEYWORDS: Trace element- Zinc, Erythrocytes, Free Radicals, Antioxidants

Pooja Sharma	* Dr. Neena Nair	R.S.Bedwal
Cell & Molecular Biology Laboratory, Department of Zoology, University of Rajasthan, Jaipur-302004,India	Cell & Molecular Biology Laboratory, Department of Zoology, University of Rajasthan, Jaipur-302004,India * corresponding author	Cell & Molecular Biology Laboratory, Department of Zoology, University of Rajasthan, Jaipur-302004,India

ABSTRACT *Although trace elements contribute < 0.01% to the total body weight but are still essential owing to the multiple functions performed by them in the biological systems. Zinc, amidst all, is quite diverse and has essential role in various aspects which contribute to health. Its estimation in blood especially erythrocytes is significant, as it can be used as pure membrane system, wherein its interaction / effect with free radicals and regulatory aspect of antioxidants can be studied which would provide an insight for various disease states due to imbalance of cellular homeostatic zinc.*

Trace element - Zinc

The nine biological trace elements viz. iron, zinc, selenium, copper, iodine, manganese, molybdenum, chromium and cobalt are considered to have a nutritional requirement for humans (Evans and Halliwell 2001; Sapota *et al.,* 2009). Although they contribute <0.01% to the total body weight but are still essential for the health of an individual (Lowe *et al.,* 2009; Hambidge *et al.,* 2010). Zinc is the second most abundant trace element (McCall *et al.,* 2000; Zhou *et al.,* 2007) and has multiple relevant functions in the biological systems as most of them are linked to zinc containing enzymes (Hambidge, 2000; Osei and Hamer, 2008). It is the most abundant intracellular metal ion found in cytosol, vesicles, organelles and nucleus (Devi *et al.,* 2014). It has earned recognition as a micronutrient of outstanding and diverse biological, clinical and global public health importance and has indispensable role in human health (Kambe *et al.,* 2004; Hambidge *et al.,* 2010). More prominently, infants, children, women and elderly person are at greater risk because of their high daily needs for vitamins and minerals and hence their mental as well as physical development may be retarded and impaired due to its reduced intake (Martin- Prevel *et al.,* 2016) leading to development of clinical or subclinical deficiency of zinc. The requirement of zinc is also enhanced where there is physical exertion (Lukaski, 2005). It is the fifth and the newest member to "top-micronutrients-to-consider-in-interventions" with iron, vitamin A, folic acid and iodine for developing countries (Food and Nutrition Bulletin, 2009).

The average adult body contains between 1.5 and 3 gm of zinc with approximately 60% present in the muscles, 30% in the bones and 6% in the skin (Plum *et al.,* 2010). The chemical properties of zinc are particularly favorable to a multiplicity of functionally significant interactions as under physiological conditions it does not undergo reduction or oxidation and exists primarily in a divalent state. Its variable coordination sphere and stereochemical adaptability help it to assume multiple coordination geometries contributing to its biochemical versatility (Vallee and Falchuk, 1993).

Zinc is required for growth, development, proliferation and differentiation (Bedwal *et al.*, 1991; Beyersmann and Haase 2001; Prasad 2008; Plum *et al.,* 2010; Kumari *et al.,* 2011a, b; Joshi *et al.*, 2014 a, b). It is a component of zinc finger proteins (Kambe *et al.,* 2004; Mocchegiani *et al.,* 2006) involved in several processes viz. DNA replication, transcription (Auld 2009), cell division, immune processes (Shankar and Prasad, 1998; Tapiero and Tew, 2003; Bhowmik *et al.,* 2010), protein synthesis, lipid metabolism, membrane stabilization against bacterial endotoxins (O'Dell 2000), antioxidant enzyme production, maintenance of lymphocyte replication, antibody production (Tapiero and Tew, 2003), receptor activity and neurophysiology (Stefanidou *et al.,* 2006), nucleic acid metabolism (Miller *et al.,* 2007), cell signaling (Frederickson *et al.,* 2005, Joshi *et al.*, 2014 a, b) and apoptosis (Troung-Tran *et al.*, 2002; Bhowmik *et al.,* 2010; Kumari *et al.,* 2011b) etc. Zinc also acts as an antioxidant, cryoprotectant and an anti-inflammatory agent (Powell 2000, Prasad 2009).

Zinc deficiency is very common and may lead to generalized impairment of many metabolic functions and optimal work performance in numerous physiological functions (Fraker, 2005). It can lead to oxidative damage in various macro-molecules and can cause the accumulation of peroxidant in several tissues. The World Health Report (2002) estimated the global prevalence of zinc deficiency as 31% ranging from 6% to 73% across WHO mortality sub-regions. Homeostatic mechanisms involve numerous proteins which normally stabilize zinc status and alteration /imbalance would lead to increased chances of variation in zinc metabolism which can be fatal. For example, acrodermatitis enteropathica in humans is a fatal disease if untreated with zinc. It is caused by a mutation in zinc transporter hzip4 (Powell, 2000; Oteiza and Mackenzie, 2005).

BLOOD

Blood is a transport medium for trace elements between organs, may be used for diagnostic purposes because it signals biochemical changes at different points in human metabolism (Kruse- Jarres and Rukgauer, 2000; Cimen, 2008). Blood cells such as erythrocytes, polymorphonuclear (PMN) and mononuclear leucocytes (MNC) as well as platelets separated from whole blood can be used to determine trace elements status. Analysis of trace element concentration in various blood cell types would provide a better in-

Volume : 6 | Issue : 10 | October 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

sight into the pathogenesis of metabolic disorders inspite of the fact that still molecular mechanisms of oxyradical mediated cellular pathogenesis is not well understood (Kruse-Jarres and Rukgauer, 2000; Jemai *et al.,* 2007).

ERYTHROCYTES

These are the most unique carriers of oxygen having rich polyunsaturated membrane lipids and iron, hence highly susceptible to oxidative stress conditions which can damage the red blood cell itself (Johnson *et al.,* 2005). Its cell membrane is an important target for radical damage (Cimen, 2008). Trace element zinc plays an important role in the structure and function of biological membranes. Human erythrocytes contain approximately 150 µmol of zinc per litre of cells and over 90% of which is bound to the enzymes-carbonic anhydrase and superoxide dismutase (Inal *et al.,* 2001). Physiologic relevance of metallothionein – a transition metal binding protein has been shown in terms of redox regulation of Zn-S interactions and coupling of zinc and redox metabolism (Maret, 2008, 2011 a, b) and has a significant role in homeostasis of essential metals viz. zinc and copper as well as detoxification of toxic metals and protection against free radicals (Kang, 2006). Cellular zinc homeostasis acts as an endogenous modulator of monocyte differentiation (Dubben *et al.*, 2010). Dietary zinc deficiency causes increased osmotic fragility in erythrocytes (Kraus, *et al.,* 1997). Integrity of cellular membranes and more particularly of red and white blood cells depends upon loosely bound ionic zinc. The antioxidant role performed by zinc and its ability to assist in stability of membranes, suggest the central role played by zinc in prevention of free-radical induced injuries properties (Kraus *et al.,* 1997).

FREE RADICALS

They are short lived in terms of milli-, micro- or nano seconds. Various cytotoxic species are formed due to univalent reduction of molecular oxygen, that is reactive oxygen species (ROS) such as superoxide anions (O2 -), hydrogen peroxide (H2O2) and hydroxyl radical (OH.) which cause oxidative damage in the cell consequently leading to irreversible injuries (Cimen 2008). Another group of reactive nitrogen species (RNS) also affects cellular function and includes nitric oxide (NO), peroxynitrite (ONOO -), nitric dioxide radical (.NO2), oxides of nitrogen etc. The overall damage caused by ROS in cell is manifested in the form of peroxidation of membrane polyunsaturated fatty acid chains, modification of DNA- formation of 8-oxo-deoxyguanosine, other oxidized DNA molecules, DNA cross links etc , carbonylation, loss of sulphydryl in proteins and host of other changes in cell composition as well as in cell membrane (Mylonas and Kouretas, 1999; Mossa ATH *et al.*, 2014). The adverse free radical reactions have been implicated in the pathogenesis of a large number of diseases such as diabetes mellitus, cancer, rheumatoid arthritis, systemic lupus erythematosus, infectious diseases atherosclerosis and neurodegenerative diseases (Taysi *et al.,* 2008; Akinola *et al.,* 2010).

ANTIOXIDANTS

To meet the challenges of the free radicals in the cells, aerobic organisms have been naturally equipped with powerful battery of mechanisms that protect them from adverse effects of lipid peroxidation and other harmful consequences. These are commonly called as antioxidant defenses (Polat *et al.,* 2007; Jennes *et al., 2007*). Antioxidants are classified into two broad divisions, depending on their solubility in water (hydrophilic) or in lipids (lipophilic). Selenium and zinc are commonly referred to as antioxidant nutrients. Although these chemical elements have no antioxidant action themselves but they are essential for the activity of some antioxidant enzymes (Imley, 2003).

ROS V/S ANTIOXIDANTS

Reactive oxygen species (ROS) are potent oxidant and contribute significantly to pathologies of various diseases. ROS mediated cellular damage cause destruction of membrane integrity and loss of cellular homeostasis. Zinc prevents ROS production and is involved in cell membrane stabilization by preventing the *in vitro* iron and copper induced breakage of DNA and inhibition of iron-initiated lipid oxidation in red blood cells (Gul *et al.,* 2006). The antioxidants are usually present in serum, erythrocytes and other tissues and organs. The antioxidant system to balance the oxidative state consists of complex system of antioxidant molecules which comprise groups of enzymatic (superioxide dismutase, catalase,glutathione peroxidase, glutathione –s- transferase, glutathione reductase etc) and non-enzymatic (vitamin C, vitamin E, metallothioneins, glutathione, zinc, flavanoids, caretenoids etc.) defense mechanisms existing in the human body (Nzengue *et al.,* 2011; Cimen, 2008; Prasad, 2013). An uncontrolled ROS generation leading to imbalanced state with antioxidant state has been observed (Nishida, 2011).

Lipid peroxidation is the first indicator of oxidative stress. Hydroperoxides generated during this process severely affects the membrane either (a) directly and through degradation to highly toxic hydroxyl radical (b) formation of stable aldehydes such as malonaldehyde on reaction with iron or copper (Halliwell and Gutteridge, 1990). Changes in primary structure of protein due to lipid oxidation products would lead to changes in secondary and tertiary structure of proteins (Meng *et al.*, 2005). Conversion of ferrous to ferric state leads to the formation of superoxide radical which would cause peroxidative damage to red cells as superoxide radical can interact with peroxides to form ·OH radicals leading to hemolysis (Wever *et al.*, 1973; Thomas *et al.,* 1978). Erythrocytic membrane has band 3 transmembrane protein which not only interacts with phospholipids at its surface but has a significant role in anion transport. Due to accumulation of malonaldehyde (a) anion transport as well as function of band 3 associated enzymes namely glyceraldehyde-3-phosphate dehydrogenase and phosphofructokinase are affected (b) polyunsaturated fatty acids of the cellular membrane are degraded disrupting the membrane integrity ultimately leading to damage to cell membrane (Steck, 1978).

Superoxide dismutases (SODs, EC 1.15.1.1) a dimeric metalloenzyme catalyzes the dismutation of the superoxide anion into molecular oxygen and hydrogen peroxide. Various types of SOD are present: MnSOD [prokaryotes & mitochondria], Cu-Zn SOD [eukaryotes –cytosol, lysosomes, nucleus & peroxisomes] and FeSOD [prokaryotes]. Almost all aerobic cells and extracellular fluids have SOD enzymes. A correlationship between SOD activity and life span of erythrocyte has been deduced by Grzelack *et al.*, (2008). Devi *et al.*, (2000) reported an increased Cu-Zn SOD activity in acute lymphocytic and non lymphocytic leukemia's which reflects its role in protecting erythrocyte from oxidative stress. Catalase (EC 1.11.1.6), a heme protein present in peroxisomes and inner mitochondria, converts O2 - which traverses through the membrane into H2O2 thereby protecting red cell as hemoglobin is a catalyst for peroxidative reactions. However, H2O2 can also cause damage under certain conditions via Haber –Weiss reaction. (Das and Banerjee, 1993). Rukmini et al., (2004) showed in-

Volume : 6 | Issue : 10 | October 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

creased antioxidant activities (SOD & CAT) as well as weak correlation with MDA level involving impairement of antioxidant defence system in the erythrocytes of schizophrenic patients. Glutathione maintains the reduced state of proteins rich in sulfur which spans the erythrocyte membrane (Bozzi et al., 1996). GPx4 reduces the phospholipid hydroperoxides in normal red cell /mammalian cells (Imai and Nakagawa, 2003) but is dependent on glutathione. Deficiency of these oxidants would potentiate oxidative damage to the erythrocyte.

Similarly, proteins which constitute a major part of the cellular components are the main targets of oxidative damage and as a consequence a variety of amino acids are modified. ROS attack cellular protein components by causing oxidation of amino acid side chains and protein backbones thereby affecting the integrity of the membrane (Zelko *et al.*, 2002). Protein carbonylation is associated with important functional changes in various structural and enzymatic proteins which play an important role in aetiology or disease progression. Among all the other biomarkers of oxidative protein damage, protein carbonyl content is the most widely used marker (Chevion *et al.,* 2000) and their elevated levels are generally not only a sign of oxidative stress but of disease-derived protein dysfunction.

Protein S-thiolation/ dethiolation, i.e. the oxidation of protein sulfhydryls to mixed disulfides and their reduction back to sulfhydryls, is an early cellular response to oxidative stress. Protein sulphydryls are also susceptible to irreversible damage by oxidative conditions. Usually in the absence of adequate antioxidant protection, these reactive sites may become useless because of this irreversible damage (Thomas *et al.,* 1992).

Although the cytosolic antioxidant system is relatively complex but the membrane itself contains only vitamin E as the major, if not the only, lipid-soluble chain-breaking antioxidant and protects it from damage by trapping the lipid peroxyl radicals (Agte *et al.,* 2004).

Enrichment of diet with combined antioxidants as vitamin C, vitamin E and β-carotene has shown to prevent elevated osmotic fragility of erythrocytes in cases of zinc deficiency (Kraus et al., 1997). Vitamin C is a well known antioxidant in the biological systems and is capable of reducing variety of oxidative compounds especially free radicals because of which it is considered as the strongest reductant. In plasma although ascorbate is highly susceptible but it gets recycled from its oxidized form in erythrocytes (Mendiratta *et al.,* 1998) which enhances the its antioxidant potential. The body must have sufficient levels of vitamin C and its deficiency may lead to scurvy and to oxidative injury resulting in necrosis or apoptosis (May *et al.,* 2000).

Conclusion

In case of trace elements as zinc, the change in physiological behavior, the effect of supplementation and its balance all need to be assessed. Particular effects between deficiency and intoxication of zinc also need to be taken into consideration while assessing zinc status. In pathological doses, zinc is non-toxic (Maret and Sandstead, 2006). The assessment of zinc nutriture is complex and have a number of chemical and functional measurements, limited sensitivity and specificity (Kruse-Jarres and Rukgauer, 2000). Importance of sufficient zinc can be estimated with the fact that even DNA instructions get misread because of its deficiency (Shankar and Prasad, 1998). It is the only transitional element which is neither cytotoxic nor systematically toxic; not even carcinogenic, mutagenic or teratogenic.

Challenge is to achieve intake of bioavailable zinc tissue level within a physiological range. Due to lack of adequate biomarkers (Wood, 2000), lack of pathognomonic clinical features, it is difficult to assess cases of zinc deficiency. Therefore, assay of cellular zinc provides more sensitive criterion for diagnosing mild deficiency of zinc. Cells are better sources reflecting long-term zinc status than rapidly turning over plasma pool (Kaur *et al.,* 2014). Global estimates have indicated that ~1/3 of the world's population live in countries where the risk of zinc deficiency is high. Zinc is a very promising trace element towards public health but it must be administered as per patient's actual requirement (Wardlaw *et al.*, 2004). Supplementation, fortification and dietary modification/diversification may altogether help in improvement of zinc intakes in whole population or groups at risk of zinc deficiency. But most important and critical area is development of better methods to assess zinc status of individuals and populations.

References-

1. Mossa, A.T.H, Heikal, T.M. & Mohafrash, S.M.M. (2014). Lipid peroxidation and oxidative stress in rat erythrocytes induced by aspirin and diazinon: the protective role of selenium. Asian J. Tropic. Biomed., 4(2): S603-S609.
2. Agte, V.V., Chiplonkar, S.A., & Nagmote, R.V. (2004). Role of vitamin-zinc interactions on *in vitro* zinc uptake by human erythrocytes. Agharkar Research Ins., 99: 99-112.
3. Auld, D.S. (2009). The ins and outs of biological zinc sites. Biometals, 22: 141-148.
4. Akinola, F.F., Oguntibeju, O.O., & Alabi, O.O. (2010). Effects of severe malnutrition on oxidative stress in Wistar rats. Sci. Res. Essays, 5:1145-1149.
5. Bedwal, R.S., Nair, N., & Mathur, R.S. (1991). Effects of zinc deficiency and toxicity on reproductive organs, pregnancy and lactation: A review. Trace Elem. Med., 8: 89-100.
6. Beyersmann, D., & Haase, H. (2001). Functions of zinc in signaling, proliferation and differentiation of mammalian cells. Biometals, 14(3-4): 331-341.
7. Bhowmik, D., Chiranjib & Kumar, K.P.S (2010). A potential medical importance of zinc in human health and chronic disease. Int. J. Pharm. Biomed. Sci., 1: 5-11.
8. Bozzi, A., Parisi, M., & Strom, R. (1996). Erythrocyte glutathione determination in the diagnosis of glucose-6-phosphate dehydrogenase deficiency. Biochem. Mol. Bio. Int., 40:561-569.
9. Chevion, M., Berenshtein, E., & Stadtman, E.R. (2000). Human studies related to protein oxidation: protein carbonyl content as a marker of damage. Free Radic. Res., 33: 99-108.
10. Cimen, M.Y. (2008). Free radical metabolism in human erythrocytes. Clinica. Chimica. Acta, 390: 1-11.
11. Das, D. & Bannerjee, R.K. (1993). Effect of stress on the antioxidant enzymes and gastric ulceration. Mol. Cell. Biochem., 125: 115- 125.
12. Devi, G.S., Prasad, M.H., Saraswathi, I., Raghu, D., Rao, D.N., & Reddy, P.P. (2000). Free radicals, antioxidant enzymes and lipid peroxidation in different types of leukemias. Clin. Chem. Acta, 293: 53-62.
13. Devi, Ch.B., Nandkishore, Th., Sangeeta, N., Basar, G., Devi, N.O., Jami, S., & Singh, M.A. (2014). Zinc in human health. IOSR-J. Dent. Med. Sci., 13(7): 18-23.
14. Dubben, S., Höuscheid, A., Winkler, K., Rink, L., & Hasse, H (2010). Cellular zinc homeostasis is a regulator in monocyte differentiation of HL-60 cells by 1β, 25-dihydroxyvitamin D3. J. Leukoc. Bi9ol., 87: 833-844.
15. Evans, P., & Halliwell, B. (2001). Micronutrients: Oxidants/ antioxidant status. Brit. J. Nutr., 85: 67-74.
16. Fraker, P.J. (2005). Roles for cell death in zinc deficiency. J. Nutr., 135: 359-362.
17. Frederickson, C.J., Koh, J.Y., & Bush, A.I. (2005). The neurobiology of zinc in health and disease. Nat. Rev. Neurosci., 6: 449-462.
18. Grezelack, A., Kruszewski, M., Macierzynsk, E., Piotrowski, L., Pulaski,

Volume : 6 | Issue : 10 | October 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

L., Rychilik, B., & Bartosz, G. (2008). The effect of superoxide dismutase knockout on the oxidative stress parameters and survival of mouse erythrocytes. Cell. Mol. Biol. Lett., 14: 23-34.

19. Gul, M., Demircan, B., Tayasi, S., Oztasan, N., Gumustekin, K., Siktar, E., Polat , M.F., Akar, S., Akcay, F., & Dane, S. (2006). Effects of both endurance training and acute exhaustive exercise on antioxidant defense mechanism in rat heart. Comp. Biochem. Physiol. Part A Mol. Integr. Physiol., 143: 239-245.
20. Halliwell, B., & Gutteridge, J.M. (1990). Role of free radicals and catalytic metal ions in human disease : An Overview. Method Enzymol., 186: 1-85.
21. Hambidge, M. (2000). Human zinc deficiency. J. Nutr., 130: 1344-1349.
22. Hambidge, K.M., Miller, L.V., Westcott, J.E., Sheng, X., & Krebs, N.F. (2010). Zinc bioavailability and homeostasis. Am. J. Clin. Nutr., 91: 1478-1483.
23. Imai, H., & Nakagawa, Y. (2003). Biological significance of phospholipid hydroperoxide glutathione peroxidase (PHGPx, GPx 4) in mammalian cells. Free radic. Biol. Med., 34(2): 145-169.
24. Imlay, J.A. (2003). Pathways of oxidative damage. Annu. Rev. Microbiol., 57: 395-418.
25. Inal, M.E., Kanbak, G., & Sunal, E. (2001). Antioxidant enzyme activities and malondialdehyde levels related to aging. Clin. Chim. Acta., 305: 75-80.
26. Jemai, H., Messaoudi, I., Chaouch, A., & Kerkeni, A. (2007). Protective effect of zinc supplementation on blood antioxidant defense system in rats exposed to cadmium. J. Trace. Elem. Med. Biol., 21: 269-273.
27. Jennes, A., Ren, M., Rajendran, R., Ning, P., Huat, Bt., Watt, F., & Halliwell, B. (2007). Zinc supplementation inhibits lipid peroxidation and the development of atherosclerosis in rabbits fed a high cholesterol diet. Free Radic. Biol. Med., 15: 559-566.
28. Johnson, R.M., Goyette, Jr. G.W., Ravindernath, Y., & Ho, Y.S. (2005). Haemoglobin autoxidation and regulation of endogenous H_2O_2 levels in erythrocytes. Free Radic. Biol. Med., 39: 1407-1417.
29. Joshi, S., Nair, N., & Bedwal, R.S. (2014 a). Dietary zinc deficiency affects dorso-lateral and ventral prostate of Wistar rats: Histological, biochemical and trace element study. Biol. Trace Elem. Res. 161(1): 91-100.
30. Joshi, S., Nair, N., & Bedwal, R.S. (2014 b) Sterological studies in prostate of dietary zinc deficient Wistar rats. Indian J. Appl. Res., 4: 566-569.
31. Kambe, T., Yamaguchi, Y., Sasaki, R., & Nagao, M. (2004). Overview of mammalian zinc transports. Cell. Mol. Life Sci., 61: 49-68.
32. Kang, Y.J. (2006). Metallothionein redox cycle and function. Exp. Biol. Med., 231: 1459-1467.
33. Kaur, K., Gupta, R., Saraf, S.A., & Saraf, S.K. (2014). Zinc: The metal of life. Comprehensive Rev. Food Sci. Food Safety, 13: 358-376.
34. Kraus, A., Roth, H.P., & Kirchgessner, M. (1997). Influence of Vitamin C, Vitamin E and β-carotene on the osmotic fragility and primary antioxidant system of erythrocytes in zinc-deficient rats. Arch. Anim. Nutr., 50: 257-269.
35. Kruse-Jarres, J.D., & Rükgauer, M. (2000). Trace elements in diabetes mellitus. Peculiarities and clinical validity of determinations in blood cells. J. Trace Elem. Med. Biol., 14(1): 21-27.
36. Kumari, D., Nair, N., & Bedwal, R.S. (2011a). Effect of dietary zinc deficiency on testes of Wistar rats: Morphometric and cell quantification studies. J. Trace Elem. Med. Biol., 25: 47-53.
37. Kumari, D., Nair, N., & Bedwal, R.S. (2011b). Testicular apoptosis after dietary zinc deficiency: Ultrastructural and TUNEL studies. Sys. Biol. Rep. Med., 57: 233-243.
38. Lowe, N.M., Fekete, K., & Decsi, T. (2009). Methods of assessment of zinc status in humans: A systematic review. Am. J. Clin. Nutr., 89: 2040-2051.
39. Lukaski, H.C. (2005). Low dietary zinc decreases erythrocyte carbonic anhydrase activities and impairs cardiorespiratory function in men during exercise. Am. J. Clin. Nutr., 81: 1045-1051.
40. Maret, W., & Sandstead, H.H. (2006). Zinc requirements and the risks and benefits of zinc supplementation. J. Trace Elem. Med. Biol., 20(1): 3-18.
41. Maret, W. (2008). Metallothionein redox biology in the cytoprotective and cytotoxic functions of zinc. Exptl. Gerontol., 43: 363-369.
42. Maret, W. (2011a). Redox biochemistry of mammalian metathionein. J. Biol. Inorg. Chem., 16: 1079-1086.
43. Maret, W. (2011b). Metals on the move: Zinc ions in cellular regulation and in the coordination dynamics of zinc proteins. Biometals., 24: 411-418.
44. Martin-Prevel, Y., Nikiema, L., Moussi, M., Ayassou, K., Lanou, H., & Allemand, P. (2016). Biological status and dietary intakes of iron, zinc, vitamin A among women and preschool children in rural Burkina Faso. PLoS One., 11(3): e0146810.doi:10.1371.
45. May, K.M., Qu, Z.C., & Cobb, C.E. (2000). Extracellular reduction of the ascorbate free radical by human erythrocytes. Biochem. Biophys. Res. Commun., 267: 118-123.
46. McCall, K.A., Huang, C., & Fierke, C.A. (2000). Function and mechanism of zinc metalloenzymes. J. Nutr., 130: 1437-1446.
47. Mendiratta, S., Qu, Z.C., & May, J.M. (1998). Erythrocyte ascorbate recycling: Antioxidant effects in blood. Free Radic. Biol. Med., 24(5): 789-797.
48. Meng, G., Chan, J.C.K., Rousseau, D., & Li-Chan, E.C.Y. (2005). Study of protein-lipid interactions at the bovine serum albumin/oil interface by raman microspectroscopy. J. Agric. Food Chem., 53: 845-852.
49. Miller, J.C., Holmes, M.C., Wang, J., Guschin, D.Y., Lee, Y.L., Rupniewski, J., Beausejour, C.H., Waite, A.J., Wang, N.S., Kim, K.A., Gregory, P.D., Pabo, C.O., & Rebar, E.J. (2007). An improved zinc-finger nuclease architecture for highly specific genome editing. Nat. Biotechnol., 25(7): 778-785.
50. Mocchegiani, E., Giacconi, R., Muti, E., Cipriano, C., Costarelli, L., Rink, L., & Malavolta, M. (2006). Zinc homeostasis in aging: Two elusive faces of the same metal. Rejuvenation Res., 9: 351-354.
51. Mylonas, C., & Kouretos, D. (1999). Lipid peroxidation and tissue damage. In Vivo., 13(3): 295-309.
52. Nishida, Y. (2011). The chemical process of oxidative stress by copper (II) and iron (III) ions in several neurodegenerative disorders. Monatsh Chem., 142: 375–384.
53. Nzengue, Y., Candeias, S.M., Sauvaigo, S., Douki, T., Favier, A., Rachidi, W., & Guiraud, P. (2011). The toxicity redox mechanisms of cadmium alone or together with copper and zinc homeostatis alteration: Its redox biomarkers. J. Trace Elem. Med. Biol., 25: 171-180.
54. O'Dell, B.L. (2000). Role of zinc in plasma membrane function. J. Nutr., 130: 1432-1436.
55. Osei, A.K., & Hamer, D.H. (2008). Zinc nutrition and tribal health in India. Tribes Tribals, 2: 111-119.
56. Oteiza, P.I., & Mackenzie, G.G. (2005). Zinc, oxidant-triggered cell signaling and human health. Mol. Aspects Med., 26: 245–255.
57. Plum, L.M., Rink, L., & Haase, H. (2010). The essential toxin: Impact of zinc on human health. Int. J. Environ. Res. Public Health, 7: 1342-1365.
58. Polat, O., Kilicoglu, S.S., & Erdemli, E. (2007). A controlled trial of glutamine effects on bone healing. Adv. Ther., 24: 154-160.
59. Powell, S.R. (2000). The antioxidant properties of zinc. J Nutr., 130(5S Suppl): 1447S-1454S.
60. Prasad, A.S. (2008). Zinc in human health: Effect of zinc on immune cells. Mol. Med., 14: 353-357.
61. Prasad, A.S. (2009). Impact of the discovery of human zinc deficiency on health. J. Am. Coll. Nutr., 28: 257-265.
62. Prasad, A.S. (2013). Discovery of human zinc deficiency: Its impact on human health and disease. Adv. Nutr., 4(2): 176-190.
63. Martin-Prevel, Y., Allemand, P., Nikiema, L., Ayassou, K.A., Ouedraogo, H.G., Moursi, M., & De Moura, F.F. (2016). Biological Status and Dietary Intakes of Iron, Zinc and Vitamin A among Women and Preschool Children in Rural Burkina Faso. PLoS One, 11(3): e0146810.
64. Rukmini, M.S., D'Souza, B., & D'Souza, V. (2004). Superoxide dismutase and catalase activities and their correlation with malonaldehyde in schizophrenic patients. Indian J. Clin. Biochem., 19(2): 114-118.
65. Sapota, A., Darago, A., Taczalski, J., & Kilanowicz, A. (2009). Disturbed homeostasis of zinc and other essential elements in the prostate gland dependent on the character of pathological lesions. Biometals, 22: 1041-1049.
66. Shankar, A.H. & Prasad, A.S. (1998). Zinc and immune function: The biological basis of altered resistance to infection. Am. J. Clin. Nutr., 68: 447-463.

Volume : 6 | Issue : 10 | October 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

67. Steck, T.L. (1978). The band 3 protein of the human red cell membrane: A review. J. Supramol. Struct., 8: 311-324.
68. Stefanidou, M., Maravelias, C., Dona, A., & Spiliopoulou, C. (2006). Zinc: A multipurpose trace element. Arch. Toxicol., 80: 1-9.
69. Tapiero, H., & Tew, K.D. (2003). Trace elements in human physiology and pathology: Zinc and metallothioneins. Biomed. Pharmacotherapy, 57: 399-411.
70. Taysi, S., Cikman, O., Kaya, A., Berna Demircan, R., Gumustekin, K., Yilmaz, A., Boyuk, A., Keles, M., Akyuz, M., & Turkeli, M. (2008). Increased oxidant stress and decreased antioxidant status in erythrocytes of rats fed with zinc-deficient diet. Biol. Trace Elem. Res., 123: 161-167.
71. The World Health Report (2002): Reducing risks, promoting healthy life. Geneva
72. Thomas, E.A., Bailey, L.B., Kauwell, G.A., Lee, D.Y., & Cousins (1992). Erythrocyte metallothionein response to dietary zinc in human. J. Nutr., 122: 2408-2414.
73. Thomas, M.J., Mehl, K.S., Pryor, W.A. (1978). The role of the superoxide anion in the xanthine oxidase-induced auto-oxidation of linoleic acid. Biochem. Biophys. Res. Commun., 83: 927-932.
74. Troung-Tan, AQ., Ruffin, R.E., Foster, P.S., Koskinen, A.M., Coyle, P., Philcox, J.C., Rofe, A.M., & Zalewski, P.D. (2002). Altered zinc homeostasis and caspase-3 activity in murine allergic airway inflammation. Am. J. Respir. Cell Mol. Biol., 27: 286-296.
75. Vallee, B.L., & Falchuk, K.H. (1993). The biochemical basis of zinc physiology. Physiol. Rev., 73: 79-118.
76. Wardlaw, G.M., Hampl, J.S., & Disilvestro, R.A. (2004). Perspective in Nutrition. Sixth Edition. Mc Graw Hill College, Boston MA.
77. Wever, R., Oudega, B., & Van Gelder, B.F. (1973). Generation of superoxide radicals during the autoxidation of mammalian oxyhemoglobin. Biochim. Biophys. Acta. 1973; 302: 475–478.
78. Wood, R.J. (2000). Assessment of marginal zinc status in humans. J. Nutr., 130: 1350-1354.
79. Zelko, I.N., Mariani, T.J., & Folz, R.J. (2002). Superoxide dismutase multigene family: a Comparison of the Cu Zn-SOD (SOD1), Mn-SOD (SOD2) and EC-SOD (SOD3) gene structures, evolution and expression. Free Radic. Biol. Med., 33(3): 337-349.
80. Zhou, Z., Wang, L., Song, Z., Saari, J.T., McClain, C.J., & Kang, Y.J. (2004). Abrogation of nuclear factor-kappa B activation is involved in zinc inhibition of lipopolysaccharide-induced tumor necrosis factor-alpha production and liver injury. Am. J. Pathol., 164: 1547-1556.