Trop J Nat Prod Res, July 2018; 2(7):303-308 **ISSN 2616-0684 (Print)**
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

The Role of Metallothionein and Some Micronutrients in the Pathogenesis of HIV Infection: A Review

Mathias A. Emokpae[1]* and Rachel I. Nimenibo-Uadia[2]

[1]*Department of Medical Laboratory Science, School of Basic Medical Sciences, College of Medical Sciences, University of Benin, Benin City, Nigeria.*
[2]*Department of Biochemistry, Faculty of Life Sciences, University of Benin, Benin City, Nigeria.*

ARTICLE INFO

Article history:
Received 12 June 2018
Revised 25 June 2018
Accepted 27 June 2018
Published online 08 July 2018

ABSTRACT

Human immunodeficiency virus (HIV) infection remains a major public health challenge especially in sub-Sahara Africa where the prevalence is highest compared to other regions of the world. The problem of micronutrients deficiency in this region is far from being resolved and has been associated with HIV disease severity, disease progression and mortality. The purpose of this review was to highlight the roles and significance of the serum levels of metallothionein and ceruloplasmin in the homeostasis of some essential elements in HIV infected subjects. Google scholar and Pubmed search engines were used to search for relevant articles which were used for this review. In HIV infection, there is an increase in the positive acute phase proteins such as ceruloplasmin and a decrease in negative acute phase reactant such as transferrin, zinc and iron. Ceruloplasmin and metallothionein help in maintaining homeostasis of essential metals in the body such as copper, zinc and iron which aid in regulation of the immune system. Various studies have shown that there is an increase in serum ceruloplasmin levels which helps to transport copper and an increase in copper leads to a decrease in serum level of zinc thereby leading to decrease in metallothionein which is induced by zinc. Supplementation of some of these essential elements has been implemented, but cautious use of trace elements supplements is suggested. Laboratory monitoring of serum levels of these elements and proteins cannot be ignored.

Keywords: Ceruloplasmin, metallothionein, essential micronutrients, human immunodeficiency virus.

Introduction

Human immunodeficiency virus (HIV) is a health challenge especially in sub-Sahara Africa, a region that harbours the highest burden of the infection.[1] The problem of micronutrient deficiencies in sub-Sahara Africa is still not resolved and commonly associated with high mortality and morbidity among HIV infected individuals. Studies have reported that micronutrients deficiencies are associated with adverse clinical outcomes during HIV infection and there is emerging evidence to suggest that micronutrient supplementation may help to reduce mortality and morbidity during HIV infection.[1] When an individual is infected with HIV, a lot of changes occur because of the unfavourable presence of the virus and the immunity of the host intensifies in an attempt to eliminate the invading pathogens by the immune system. This immune response alters the general immune mechanism especially the antioxidant and inflammatory systems in an attempt to eliminate the invading organism which over time affects the whole body.[2] These processes eventually deplete tissue micronutrient reserves. To maintain the integrity of the immune system, it is important to manage micronutrient levels in HIV infection.[2] Essential micronutrients are required for several body functions and well-being of the immune system. The co-existence of micronutrient deficiencies and HIV infection often exhibit complex interactions involving several proteins including metallothionein and ceruloplasmin.[3] The immune-modulatory functions of micronutrients such as zinc, selenium and copper could influence the susceptibility to the course and disease progression in HIV infection.[3] Some of the essential elements could inhibit viral replication; act as antioxidants while others help to regulate immune responses of the infected individuals. Although several studies have reported on micronutrient deficiencies in HIV infection, information on metallothionein as stress-response protein with immune-modulatory function and ceruloplasmin as acute phase protein that possesses antioxidant properties cannot be over emphasized. The objective of this review was to highlight the roles of metallothionein, ceruloplasmin and some micronutrients in the pathogenesis of HIV infection and the need to maintain adequate supply of these nutrients in order to prevent the consequences associated with their deficiencies.

HIV and host interaction

In HIV infection (as with most viruses), the most important factors to consider are genomic alterations by the virus, nutritional status and optimum function of the host immune system.[3] The life-cycle of a virus begins from its entry into a host; then reaches the susceptible target cell, multiply, causing cell injury and ultimately cell death.[3]

The overall effect of infection with HIV and its interaction with the body's natural response mechanisms is a severe damage to the immune system, destroying the means by which the human body naturally defends itself against infections. Following entry into the host, HIV is disseminated via the blood and circulatory system to different tissues in the body. From the moment of infection, the virus replicates at an extremely rapid rate causing the immune system to detect its presence and mount an immediate antibody response. This usually occurs within two to four weeks of infection and is referred to as seroconversion (because antibodies to HIV can be detected in the blood).[4] Early in the course of infection, HIV is disseminated to the lymphoid tissues. Lymph vessels carry infectious agents to the lymph nodes. These nodes

*Corresponding author. E mail: mathias.emokpae@uniben.edu
Tel: +2348034511182

Citation: Emokpae and Nimenibo-Uadia. The Role of Metallothionein and Some Micronutrients in the Pathogenesis of HIV Infection: A Review. Trop J Nat Prod Res. 2018; 2(7):303-308. doi.org/10.26538/tjnpr/v2i7.1

are located throughout the body and contain a sieve-or mesh-like structure of follicular dendritic cells (FDCs) in their germinal centres, which trap bacteria, fungi, and viruses (including HIV).[5] The lymph nodes are also the site of a concentration of immune system cells, including T -lymphocytes (the cells which orchestrate the immune response). As viruses are trapped in greater concentrations, they infect the T-lymphocytes and other cells in the lymph nodes. Eventually the FDC network completely breaks down. This destruction of lymph node architecture has been observed in lymph node biopsies.[6] Finally, with the complete destruction of the lymph nodes, viruses, bacteria, and fungi spill over into the blood stream and around the body. At this stage, levels of HIV are so high that the virus is able to infect and destroy CD4 T- lymphocytes at a faster rate than the body is able to produce new immune cells (including CD4 T -lymphocytes). This leaves the body unable to mount an effective immune response against these pathogens, including human immunodeficiency virus.

During the early stage of infection, the levels of HIV RNA (a marker of HIV infection) rise steeply, mostly due to high rates of viral replication and resulting in large amounts of virus in the blood. Overall, the level of the virus in the body is seen to rise over time. Concurrently, CD4 counts decline gradually during the same period. Whilst these two markers of infection are the most accurate determinants of the status of infection, changes in other laboratory markers are often observed. Typically, these include an increase in the levels of p24 antigen, acute phase proteins, beta-2 microglobulin and a decrease in the levels of p24 antibody, haemoglobin, neutrophils, platelets as well as decrease in the synthesis of normal blood proteins such as transthyretin (TTR, formerly called prealbumin), retinol binding protein (RBP), cortisol binding globulin, transferrin and albumin, (which represent the negative acute phase proteins), lymphocytes, and interleukin-2-receptors.[7] As the infection continues, viral load and replication rates reach such a magnitude that lymphoid tissues are completely destroyed and the turnover of CD4 T-lymphocytes cannot match the destructive actions of the virus. Thus, CD4 cell counts are seen to decline at an increasingly faster rate and, with a weakening immune system, levels of viral RNA begin to increase once again. These virological and immunological events mark the onset of the more advanced stage of infection, characterized by the onset of clinical symptoms. At this stage of infection, viral load in individuals may be extremely high, around one million copies/ml, although individual variation is significant[8]. Although, CD4 cell counts may also vary, individuals with CD4 counts below 200 cells/mm^3 are at the greatest risk of developing opportunistic infections (note that CD4 cell counts of healthy individuals are usually between the range of 500-1500 cells/mm^3).[8]

It should be noted that at any of these steps within the life cycle the course of the virus can be aborted by several host defense mechanisms. A major factor that limits the host immune defense is malnutrition. Malnutrition determines the susceptibility of an individual to infectious diseases and disease progression. The increased susceptibility and disease progression in malnourished hosts may be attributed to an impaired immune response. Malnutrition can lead to deficiencies of essential micronutrients, impaired immune response by inducing a less effective ability to challenge the invading virus. Studies have shown that both the host and the invading pathogens are affected by malnutrition.[9] Nutritional deficiencies could result from inadequate intake of major food components or essential micronutrients. Deficiency of any of the essential elements can lead to improper body function.

Methodology

Pubmed and google search were used to search for literatures on metallothionein, micronutrients and HIV infection. A total of 89,400 articles were initially obtained but 75 most relevant articles were included in the review. These articles were retrieved between April and May 2018.

Metallothionein

Metallothionein (MT) is a low molecular weight, metal binding protein that is rich in cysteine.[10] It is the single most abundant group of intracellular zinc-binding proteins in eukaryotic cells and 5 to 10% of zinc in human hepatocytes is bound to MT. Metallothionein has long been associated with resistance to toxicity resulting from exposure to toxic metals and other generators of reactive oxygen species.[10] Their capacity to interact directly with metal ions and free radicals have been taken as evidence that they protect by acting simply as sacrificial scavengers to intercept and directly inactivate toxic molecules.[10] More recently, it has been suggested that MT plays an indirect role of controlling zinc bioavailability to zinc-requiring proteins that act in a broad range of physiological events, including proteins that themselves directly mediate resistance to toxic events and those that act indirectly by receiving and transducing extracellular signals that alter cellular resistance to toxicity, transcription factors, hormone receptors, metalloproteinases, superoxide dismutase and catalase, among others.[10] The synthesis of the protein is directly induced by stress, toxic metals like cadmium and essential trace elements such as zinc, copper and the protein bind to these metals.[4] It was believed that MT functions in the detoxification of toxic metal and in the metabolism of essential metals such as zinc and copper.[5,6] It was also suggested that MT plays vital antioxidant role because of the many sulfhyryl groups as does glutathione. Studies have shown that MT can mop-up free radicals such as hydroxyl and superoxide produced by the xanthine-xanthine oxidase reactions [7] and inhibits lipid peroxidation [8]. Metallothionein has been reported to modulate immune activities in-vitro,[11] modify the severity of chronic inflammatory diseases [12] and auto-immune diseases.[4,5] Some authors have reported that manipulation of MT expression (MT deficiency or excess) can enhance host defense against *Listeria monocytogenesis*.[13]

Metallothionein can be induced by stressors whether physiological, biochemical, radiation or drugs. Radiation and high oxygen tension have been reported to cause induction of MT synthesis.[14] An injection of peroxidative agents such as carbon tetrachloride (CCl_4), paraquat and acetaminophen induced MT production in experimental mice.[15] Any condition that promotes the induction of MT is potentially capable of inducing lipid peroxidation. Other researchers have reported dissimilar functionality between MT from different origins in the body. In-vivo studies have shown that cardiac MT prevents lethal toxicity and lipid peroxidation induced by the administration of Adriamycin.[15] But hepatic MT pre-induced with zinc failed to prevent CCl_4-induced lipid peroxidation.[16] These authors concluded that it was not completely clear whether MT plays a protective role against free radicals in-vivo but induction of MT synthesis by CCl_4 was independent of lipid peroxidation, free radical generation and glutathione metabolism in the liver [16]

Caeruloplasmin

Ceruloplasmin is a blue plasma α_2-glycoprotein that is synthesized primarily in hepatocytes which is involved in the transport of copper throughout the body.[15] It was first described in 1948. It is the major copper-carrying protein in the blood and it exhibits a copper-dependent oxidase activity, which is associated with possible oxidation of Fe^{2+} (ferrous iron) into Fe^{3+} (ferric iron), therefore assisting in its transport in the plasma in association with transferrin which can only carry iron in the ferric state. Ceruloplasmin in humans is encoded by the ceruloplasmin gene which has been mapped to chromosome 3q24.[15] It is the product of an intragenic triplication and is composed of three homologous domains with an estimated molecular weight of 151 kDa and has six or seven cupric ions per molecule.[15] Two splice variants, CP-1 and CP-2, have differential expression in specific tissues. Ceruloplasmin mRNAs are expressed in human liver, macrophages and lymphocytes.[15] Another protein, hephaestin, is noted for its homology to ceruloplasmin and also participates in iron and probably copper metabolism.[15] Aceruloplasminemia is an autosomal recessive disorder of iron metabolism characterized by a complete deficiency of ceruloplasmin ferroxidase activity due to mutations in the ceruloplasmin gene.[16]

Apart from transport function, the copper atom of ceruloplasmin is essential for copper utilization in the biosynthesis of cytochrome C oxidase and also ceruloplasmin can transfer copper to metal- free superoxide dismutase. In addition, it has been shown to act as an enzyme, a serum ferroxidase playing a major role in oxidizing iron (II) to iron (III) in serum and at the cell surface, thereby assisting in its transport in the plasma in association with transferrin, which can only carry iron in the ferric state. It thereby converts the toxic ferrous form to its non-toxic ferric form.[15]

During acute phase of an inflammatory response as occur in HIV infection, several changes occur in the production of the plasma cuproprotein ceruloplasmin by the liver. Plasma caeruloplasmin is an acute phase protein that possesses antioxidant properties and plays vital

role in the regulation of iron release from cells.[17] In inflammation, metals accumulate in the liver due to the increased synthesis of MT. Studies have demonstrated that cytokines especially interleukin 1(IL-1) and interleukin 6(IL-6) were responsible for the up-regulation of MT synthesis in the liver.[8,15,16] The increased synthesis of MT during inflammation can lead to an elevation of available intracellular copper pool. These increased copper levels could facilitate the regulation of ceruloplasmin synthesis.[15] Even though the function of MT is not completely known, a role as reservoir of metals is generally accepted.[16,17] A close interaction between MT and ceruloplasmin in synthesis and functions has been proposed.[18] Cytoplasmic MT-derived copper may be released by glutathione reduction and then transported into the Golgi or endoplasmic reticulum by the P-type ATPase copper transporter and is incorporated into ceruloplasmin.[10,18] For this mechanism to be relevant in acute phase response, there has to be a coordinated increase in the transcription of MT and ceruloplasmin [18,19]. The modulation of acute phase protein synthesis is primarily achieved through cytokine-induced up-regulation in mRNA expression of the acute phase protein genes in the liver.[19] It has been reported that MT-2mRNA expression and (not MT-1) was induced by IL-1 in the human hepatoma cell line (HePG2 cells) but several others observed that IL-1 indeed induced the synthesis of MT-1, MT-2 and ceruloplasmin expressions.[18, 20]

Regulation of metallothionein by zinc

The most important factor in the modulation of MT is the amount of zinc intake.[21] Zinc deficiency is associated with poor wound healing, growth retardation, hair loss and weak immune function.[22] When zinc levels fall, skin rash, abdominal pain, loss of appetite, diarrhea and impaired taste and smell could occur. When the host's stores of zinc are depleted plasma MT is degraded to provide plasma zinc. Zinc supplementation however, can restore MT levels.[21,22] A cautious use of zinc supplement is advised because if zinc is administered for too long, it can cause depigmentation of hair and skin. In addition, excess zinc can result to copper deficiency. Copper apart from being transported by ceruloplasmin, it also binds to albumin and MT. If ceruloplasmin levels are low, free copper increases to toxic levels and results in zinc deficiency. When levels of MT and zinc bound by MT are adequate, glutathione mediates the transfer of zinc to MT. On the other hand, glutathione also oxidizes the sulfhydryl groups of MT and releases zinc to enzymes.[23] Therefore, MT, ceruloplasmin and glutathione are very important in maintaining adequate zinc levels and immune system in HIV infection.

Role of trace elements on the immune system

The immune system helps to maintain adequate physiological integrity of the body by eliminating any invading foreign agent. This the body does through innate and/or acquired immunity, a complex process involving coordinated efforts of several cell types and their secretory products such as macrophages, T and B-lymphocytes. Macrophages might be among the cells of first line of defense because of their phagocytic, cytotoxic and secretory activities. Any invading agent is phagocytized and digested by macrophages and the macrophages may be damaged in the process. Micronutrients such as zinc, selenium, copper, and vitamins do influence several components of innate immunity. These micronutrients play key roles in the dynamic of oxidant-mediated tissue injury and phagocytic cells produced reactive oxidants as part of the defense mechanism. For the cells that participate in innate immunity to function optimally, adequate supply of essential micronutrients is required. For example, deficiency of zinc may reduce natural killer cell function, but zinc supplementation can enhance their functions.[24]

The effector cells of the immune system are the T and B-lymphocytes. Whereas B-lymphocytes produce specific antibodies in response to antigen, T-lymphocytes help B-cells in antibody production as well as mediating cellular immune response. Micronutrient deficiencies could complicate malnutrition and other systemic diseases. Malnutrition is a composite syndrome of multiple nutrient deficiencies. Five concepts have been proposed to explain the interrelationship of micronutrient deficiencies and their effects in the host. They are; (i) changes in immune responses occur early in the course of inadequate micronutrient intake (ii) the extent of immunological impairment depends on the type of deficient micronutrient, its interactions with other essential nutrients, the severity of deficiency, presence of infection and age of the individual involved, (iii) immunological derangement predicts outcome of disease progression and mortality (iv) excessive intake also causes impaired immune responses (v) tests of immune-competence are important in the assessment of physiological needs and in the assessment of safe lower and upper limits of micronutrient consumption [25] . Studies have shown that HIV infection exacerbates the release of pro-oxidants, cytokines and other reactive oxygen species resulting in the increased utilization of antioxidants such as vitamin E, C, beta-carotene and micronutrients such as zinc, selenium, manganese, copper and iron. The imbalance between the production of free radicals and the presence of adequate antioxidants causes oxidative stress which further damage biomolecules and accelerate HIV replication.[25,26] Some authors have demonstrated that deficiencies of nutrients could affect immune function, favours viral expression and replication leading to increased morbidity and mortality.[27]

Cytokines are necessary for immune system to function optimally. Cytokines are soluble glycoproteins which are secreted by cells of the immune system and help to regulate immune response via specific receptors.[28] It was reported that cytokines secretion profiles correlate well with the specific functions of helper T (Th)1 and Th 2 cells. These are the major subsets of fully differentiated $CD4^+$ Th cells. The Th1 cells secrete interferone-gamma (IFN-γ), IL-2 and tumour necrosis factor-beta (TNF-β). These are responsible for cell-mediated inflammatory reactions, delayed-type hypersensitivity and tissue injury in infection.[28] The Th-2 cells on the other hand secrete IL-4, IL-5, IL-6, IL-10 and IL-13 and are associated with B-cells antibody production. The secretion functions of both Th-1 and Th-2 are cross-regulated by IFN-γ and IL-10.[29-33]

In HIV infection, a Th-1type response is associated with recovery from infection while a Th2-type response correlates with disease severity and progression.[34,35] Studies have shown that viruses have the ability to subvert or impair the host immune response to different degrees. This impairment of immune system most often leads to increased susceptibility of individuals to pathogenic viruses.

Impact of antioxidants deficiencies in HIV infection

Viral infection triggers inflammation and inflammation induces the secretion of cytokines and free radical generation. Oxidative stress has been reported in HIV infection.[36-38] The impact of antioxidant depletion is often seen at cellular levels and products of lipid peroxidation are toxic to the host. When cell membranes are damaged, these toxins are released into the body. For example, deficiency of glutathione affects liver detoxification function.[37] Supplementation of antioxidants has been suggested in persistent viral infection. Studies have shown that the most important antioxidant that needs to be restored and maintained in HIV infection is glutathione.[37,38] Essential elements such as copper, zinc, selenium and manganese act as co-factors of antioxidant enzymes which neutralize free radicals generated during oxidative stress [3]. Interestingly, a delicate balance needs to be maintained for redox trace elements such as copper which can initiate free radical generation and also as cofactor for copper-zinc superoxide dismutase. Metal chelators such as ceruloplasmin plays vital role to curtail the reactive copper ion. Selenium-deficient mice were reported to be susceptible to infection with *coxsackievirus* and *influenza virus*.[3] The immune system can be changed in selenium deficient animals as well as the viral pathogen itself. Genome sequencing of viral isolates from selenium-deficient mice has been shown to demonstrate mutations in the viral genome of coxsackievirus and influenza virus.[3] These alterations in the viral genome were associated with increased pathogenesis of the virus.[3,36] Several studies have demonstrated the antioxidant role of zinc.[37,38] Zinc ions may either replace redox active molecules like iron and copper at critical sites in cell membranes and proteins or it may induce the synthesis of metallothionein that protects against free radicals generation.[36,38]

Impact of trace elements deficiencies in HIV infection

Studies have shown that during most viral infections, both plasma and tissues levels of trace elements are altered.[39,40] Selenium deficiency in HIV infection has been associated with disease progression and mortality in infected persons.[39-41] Selenium may be also needed for the replication of the HIV and thus can deplete host selenium levels.[41] Selenium supplementation may down-regulate the abnormally high levels of IL-8 and TNF-α observed in HIV infection.[42,43] This high levels of IL-8 and TNF-α have been linked with neurological damage, Kaposi sarcoma, wasting syndrome and increased viral replication.[42,43] The impact of selenoprotein glutathione peroxidase on the inhibition of

HIV activation has been reported.[38,42,43] Increased expression of the enzyme can stimulate viral replication and the appearance of cytopathic effects associated with disease severity.

Zinc supports a healthy immune system and is essential for wound healing, the sense of taste and smell and for DNA synthesis.[44-46] Zinc often remains intracellular and participates in several physiological mechanisms. Adequate zinc level is necessary for T-cell proliferation, maturation, differentiation, lymphocyte response to mitogens, apoptosis of lymphoid and myeloid cells, gene transcription and biomembrane functions.[47,48] The immune system is adversely affected by even moderate degrees of zinc deficiency. Severe deficiency reduces immune function.[49] Primary and secondary antibody responses are depressed in zinc deficiency and generation of splenic cytotoxic T-cells is reduced after immunization.[50] Zinc supplementation given to zinc deficient individuals led to increased levels of T-cell lymphocyte population and the ability of lymphocytes to fight infection was improved.[3] Avoidance of high doses of zinc was advised because zinc can cause negative effects on immune cells resembling the changes that occur in deficiency.[50] Zinc deficiency can alter immune function from Th-1 response to Th-2 response thereby adversely influencing the course of the disease.[51] Low-dietary zinc intake has been regarded as an independent predictor of mortality in HIV infected drug users. Both deficiency and excess of zinc in HIV infection was associated with declining CD4 cell count and reduced survival.[52]

Prevalence of micronutrient deficiencies among HIV infected individuals.

In HIV infection, micronutrient deficiencies and deficiencies of other nutrients that affect the immune system are vital biochemical factors that lead to disease severity, risk of opportunistic infections and increased mortality.[50,51] Multiple micronutrient deficiencies were reported to be common among individuals living with HIV infection.[38,53] This may be attributed to inadequate dietary intake of micronutrients and low circulating micronutrients levels. The micronutrient needs may be higher among HIV infected individuals than non-infected persons.[53] Several authors have reported that most HIV infected persons consume less than the Recommended Dietary Allowance (RDA) of several micronutrients.[53-55] The RDA is the quantity of a nutrient that is regarded as adequate to meet the nutrient needs of a healthy individual. Studies have shown that micronutrient intake at the level of the RDA may be insufficient for HIV infected adults.[54,55] Some have reported that micronutrient deficiencies were common even among HIV-infected subjects on anti-retroviral drugs.[56,57] Low serum micronutrient levels, consistent with deficiency have been reported among HIV-infected subjects in Ethiopia[57] pregnant women in Malawi,[57,58] and in children in Uganda.[59] Low serum zinc levels were reported by several authors in HIV infected adults.[61-63] Low plasma selenium levels were also reported in HIV-infected adults.[64,65] It should be noted that micronutrient concentrations in the blood are affected by how much of the micronutrients that are present in the body and by infection which increases the levels of some (such as ferritin) and decreases the levels of others (such as vitamins and zinc). This may make the interpretation of blood levels of micronutrients difficult in some cases. In HIV positive homosexual men, low serum zinc levels were associated with HIV disease progression.[66,67] Some authors have suggested that serum zinc levels should be interpreted with caution in patients with inflammation since zinc is a negative acute phase reactant in the blood.[53] Low plasma selenium levels have been associated with accelerated progression of HIV disease among adults,[68] pregnant women in Tanzania,[69] children and children born to HIV infected mothers in Tanzania.[70,71]

Significance of serum metallothionein and ceruloplasmin levels in HIV infection

Ceruloplasmin has a principal function of transporting and delivery of copper to the tissue,[72] which is increased during inflammation or stress. Copper concentrations, unlike iron and zinc, increase as part of the acute-phase response. Such changes are a direct result of increased hepatic synthesis of ceruloplasmin, the major copper binding protein, mediated by cytokines IL-1, IL-6 and IL-8 [7.] Elevated ceruloplasmin concentrations during illness are postulated to be beneficial since ceruloplasmin scavenges free radicals and helps to maintain iron in the reduced state, i.e. it functions as an antioxidant.[73] An increase in serum copper level can lead to a decrease in zinc level due to the antagonistic effect of the metals. Another intriguing role of copper is the promotion of angiogenesis for facilitating tumor to progress, thus leading to cancers associated with HIV infection.[74]

Metallothionein increases the hepatic resistance against metal toxicity and may enhance intracellular metal ion binding capacity.[7,38] Together with decreased hepatocytic secretion of albumin (another zinc transporter) and of transferrin and lactoferrin, this causes decreased serum zinc and iron values.[38] The latter is regarded as beneficial for the infected organism, since iron is essential for microbial growth and reproduction. Low zinc also stresses the gut and can lead to poor digestion and malabsorption.[7] The several functions described above which are associated with essential elements could manifest when the homeostasis levels of these proteins are not maintained.

Zinc deficiency in HIV infection impairs T-lymphocyte cell mediated immunity (CMI). Zinc deficiency causes an imbalance between T-helper cell 1 and T-helper cell 2 functions with proportionally greater impairment of cell mediated immunity and prevents regeneration of new CD4 T-lymphocytes.[74] HIV infection, similarly, results in dysregulated cytokine balance with shift from Th1 systemic cellular host defense cytokines (IL-2, IFN-gamma) to Th2 humoral response cytokines (IL-4, IL-5, IL-6, IL-10), even before loss of CD4 lymphocytes. The HIV nucleocapsid protein contains two highly conserved zinc fingers, crucial for proper core assembly and viral replication.[75]

Conclusion

Ceruloplasmin level is increased in HIV infection due to acute response to the infection and oxidative stress. The increased ceruloplasmin level leads to elevated copper thereby reducing zinc and iron levels in circulation. The low serum zinc levels can lead to degradation of metallothionein in attempt to restore homeostasis. The depletion of metallothionein and zinc levels result in lowering of the immune function, promoting reduce differentiation of CD4 cells and disease progression.

Conflict of interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

References

1. Chege PM, Muthamia OG. Level of micronutrient supplements uptake among people living with HIV/AIDS in Kayole, Nairobi County, Kenya. J AIDS HIV Res. 2017; 9(4):74-80.
2. Doddigaria Z, Lakshmi LJ, Ahmad J, Faisal M. Oxidative stress in HIV in relation to metals.In: HIV/AIDS oxidative stress and Dietary Antioxidants. Academic Press, 2018.63-74 p.
3. Chaturvedi UC, Shrivastava R, Upreti RK. Viral infections and trace elements: A complex interaction. Curr Sci. 2004; 87(11):1536-1554.
4. Yoshida T, Okuda K, Xin K Q, Tadokoro K, Fukushima J, Toda S, Hagiwara E, Hamajima K, Koshino T, Saito T Activation of HIV-l-specific immune responses to an mv -1 vaccine constructed from a replication-defective adenovirus vector using various combinations of immunization protocols. Clin Experiment Immunol 2001; 124(3): 445-452.
5. McMichael AJ, Rowland H, Jones SL. Cellular immune responses to HIV. Nature. 2001; 410(6831): 980-987.
6. Orenstein JM, Yoder C, Fox C, Polis MA, Metcalf JA, Kovacs JA, Falloon J, Walker RE, Masur H, Lane HC, Davey RT.. Rapid activation of lymph nodes and mononuclear cell HIV expression upon interrupting highly active antiretroviral therapy in patients after prolonged viral suppression.AIDS 2000; 14(12):1709-1715.

7. Gruys E, Toussaint MJM, Niewold TA, Koopmans SJ. Acute phase reaction and acute phase proteins. J Zhejiang Uni Sci B. 2005; 6(11):1045–1056.
8. Gompels M, Dunn DT, Phillips A, Dooley D, Burgh TA, Anderson J, Post F, Pillay D, Gazzard B, Hill T, Johnson M, Gilson R, Bansi L, Easterbrook P, Fisher M, Walsh J, Orkin C, Ainsworth J, Leen C, Sabin C; UK Collaborative HIV Cohort (UK CHIC) Study. Does discordancy between the CD4 count and CD4 percentage in HIV-positive individuals influence outcomes on highly active antiretroviral therapy? Infect Dis. 2012; 205:540-547.
9. Beck MA, Levander OA, Handy J. Selenium deficiency and viral infection. J Nutr. 2003; 133:1463S-1467S.
10. Kavitha VS, George SD. Metallothioneins: Emerging Modulators in Immunity and Infection. Inter J Mole Sci. 2017; 18:2197.
11. Yin X, Knecht DA, Lynes MA. Metallothionein mediates leukocytes chemotaxis. BMC Immunol. 2005; 6:21.
12. Devisscher L HP, Lynes M, Waeytens A, Cuvelier C, De Vos F, Vanhove C, Vos MD, Laukens D. Role of metallothioneins as danger signals in the pathogenesis of colitis. J Pathol. 2014; 233:89-100.
13. Emeny RT, Kasten-Jolly J, Mondal T, Lynes MA, Lawrence DA. Metallothionein differentially affects the host response to listeria infection both with and without an additional stress from cold-restraint. Cell stress chaperones 2015; 20(6):1013-1022.
14. Hidalgo J, Campmany L, Borras M, Garvey J S, Armario A. Metallothionein response to stress in rats: Role in free radical scavenging. Am J Physiol. 1988; 255: E518-524.
15. Manto M. Abnormal copper homeostasis: Mechanisms and Roles in Neurodegeneration. Toxics 2014; 2:327-345.
16. Kono S, Miyajima H. Molecular and pathological basis of aceruloplasminemia. Biological Res. 2006; 39(1): 15-23.
17. Bento I, Peixoto C, Zaitsev VN, Lindley PF. Caeruloplasmin Revisited:structural and functional Roles of various Metal cation-binding sites . Acta Crystallogr D Biol Crystallogr. 2007;. 63(pt.2):240-248.
18. Daffada AI, Young SF. Coordinated regulation of Ceroloplasmin and metallothionein mRNA by interleukin-1 and copper in HepG2 cells. FEBS Lett 1999; 457:214-218.
19. Cherian MG, Jayasurya A, Bay BH. Metallothioneins in human tumors and potential roles in carcinogenesis. Mutat Res. 2003;. 533: 201–209.
20. Cousins RJ, Leinart AS. Tissue specific Regulation of transferrin gene expression. FASEB J. 1988; 2(13): 2884-2890.
21. Balfour L, Spaans JN, Fergusson D, Huff H, Mills EJ, la Porte CJ, Walmsley S, Singhal N, Rosenes R, Tremblay N, Gill MJ.. Micronutrient deficiency and treatment adherence in a randomized controlled trial of micronutrient supplementation in ART-naïve persons with HIV. PloS one. 2014; 9(1):e85607.
22. Baum MK, Campa A, Lai S, Martinez SS, Tsalaile L, Burns P, Farahani M, Li Y, Van Widenfelt E, Page JB, Bussmann H. Effect of micronutrient supplementation on disease progression in asymptomatic, antiretroviral-naive, HIV-infected adults in Botswana: a randomized clinical trial. JAMA 2013;10(20):2154-2163.
23. Shaw W. Metallothionein update. New Dev. 2009; 8(4):1.
24. Erickson KL, Medina EA, Hubbard NE. Micronutrients and innate immunity. J Infect Dis. 2000;182: S5-S10.
25. Oguntibeju OO, van den Heever WMJ, van Scalkwyk FE. The interrelationship between nutrition and immune system in HIV infection: A review. Pak J Biol Sci. 2007; 10(24):4327-4338.
26. Nunnari G, Coco C, Pinzone MR, Pavone P, Berretta M, Di Rosa M, Schnell M, Calabrese G, Cacopardo B. The role of micronutrients in the diet of HIV-1-infected individuals. Front Biosci. (Elite Ed); 2012; 4:2442-2456.
27. Bhutta ZA, Salam RA, Das JK. Meeting the challenges of micronutrient malnutrition in the developing world. Br Med Bull. 2013; 106:7-17.
28. Abbas AA, Lichtman H, Pober J. Innate immunity in cellular and Molecular Immunology. W. B., Saunders (4th Edition), Philadelphia. 2000 pp. 270-290.
29. Powrie F, Coffman RL. Cytokine regulation of T-cell function: potential for therapeutic intervention. Immunol Today 1993; 14:270–275.
30. Mosmann TR, Sad S. The expanding universe of T cell subsets: Th1, Th2 and more. Immunol Today 1996; 17:138-146.
31. van der Poll T, Jansen J, Levi M, ten Cate H, ten Cate JW, van Deventer SJH. Regulation of interleukin 10 release by tumour necrosis factor in humans and chimpanzees. J Exp Med. 1994; 180:1985-1988.
32. Shrivastava R, Upreti RK, Seth PK, Chaturvedi U C. Effects of chromium on the immune system. FEMS Immunol Med Microbiol. 2002: 34:1–7.
33. Chaturvedi UC, Dhawan R, Mukerjee R. Immunosuppression and cytotoxicity of dengue infection in the mouse model. In Dengue and Dengue Haemorrhagic Fever (eds Gubler, D. J. and Kuno, G.), CAB International Press, Wallingford, UK; 1997. 289–309 p.
34. Chaturvedi UC. Shift from a Th1-type response to Th2-type in dengue haemorrhagic fever. Curr Sci. 1999; 76: 63–69.
35. Chaturvedi UC, Agarwal R, Elbishbishi E A, Mustafa AS. Cytokine cascade in dengue haemorrhagic fever: implications for pathogenesis. FEMS Immunol Med Microbiol. 2000; 28:183–188.
36. Gutowski M, Kowalczyk S. A study of free radical chemistry: their role and pathophysiological significance. Acta Biochim Pol. 2013; 60(1):1–16.
37. Augusto O, Miyamoto S. Oxygen radicals and related species. In: Principles of Free Radical Biomedicine, K. Pantopoulos and H. M. Schipper, Eds.Nova Science Publishers. 2011. 1–23 p.
38. Ivanov AV, Valuev-Elliston VT, Ivanova ON, Kochetkov SN, Starodubova ES, Bartosch B, Isaguliants MG. Oxidative Stress during HIV Infection: Mechanisms and Consequences. Oxid Med Cell Longevity,2016; 2016:1-18.
39. Baum MK. High risk of HIV-related mortality is associated with selenium deficiency. J Acquir Immune Defic Syndr Hum Retrovirol. 1997; 15:370–374.
40. Patrick L. Nutrients and HIV; Part One–Beta carotene and selenium. Altern Med Rev. 1999; 4:403–413.
41. Campa A, Shor-Posner G, Indacoche F, Zhang G, Lai H, Asthana D, et al. Mortality risk in selenium-deficient HIV-positive children. J Acquir Immune Defic Syndr Hum Retrovirol, 1999; 15: 508–513.
42. Baum M K, Miguez-Burbano M J, Campa A, Shor-Posner G. Selenium and interleukins in persons infected with human immunodeficiency virus type 1. J Infect Dis. 2000; 182: S69–S73.
43. Taylor E W. Nutrition, HIV and drug abuse: the molecular basis of a unique role for selenium. J Acquir Immune Defic Syndr. 2000; 25:S53–S61.
44. Prasad AS. Zinc deficiency in women, infants and children. J Am. Coll. Nutr. 1996; 15:113–120.
45. Hambidge K M. Mild zinc deficiency in human subjects. In: Human Biology (ed. Mills, C. F.), Springer-Verlag, New York, 1989, pp. 281–296.
46. King JC, Keen CL. Zinc. In: Modern Nutrition in Health and Disease (eds Shils, M. E), Williams & Wilkins, Baltimore,9th edn, 1999, 223–239 p.
47. Food and Nutrition Board, Institute of Medicine, Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc, National Academy Press. Washington DC, 2001, 1-9 p.
48. Beck FW, Prasad A S, Kaplan J, Fitzgerald J T, Brewer G J. Changes in cytokine production and T cell subpopulations in experimentally induced zinc-deficient humans. Am J Physiol. 1997; 272:E1002–E1007.
49. Shankar AH, Prasad AS. Zinc and immune function:The biological basis of altered resistance to infection. Am J Clin Nutr. 1998; 68: 447S–463S.

50. Baum MK, Shor-Posner G, Campa A. Zinc status in human immunodeficiency virus infection. J Nutr. 2000; 130: 1421S-1423S.
51. Spreitsma JE. Zinc controlled Th1/Th2 switch significantly determines development of diseases. Med Hyp. 1997; 49: 1-14.
52. Baum M K, Campa A, Lai S, Lai H, Page J B. Zinc status in human immunodeficiency virus type 1 infection and illicit drug use. Clin Infect Dis. 2003; 37:S117-S123.
53. De Pee S, Semba RD. Role of nutrition in HIV infection: Review of evidence for more effective programming in resource-limited setting. Food Nutr Bull. 2010;31(4):S313-S344.
54. Baum MK, Shor-Posner G, Bonvehi P, Cassetti I, Lu Y, Mantero-Atienza E, Beach RS, Sauberlich HE. Influence of HIV-infection on vitamin status and requirements. Ann N Y Acad Sci. 1992; 669:165-173.
55. Woods MN, Spiegelman D, Knox TA, Forrester JE, Connors JL, Skinner SC, Silva M, Kim JH, Gorbach SL.Nutrient intake and body weight in a large HIV cohort that includes women and minorities. J Am Diet Assoc 2002;102:203-211.
56. Kassu A, Andualem B, Van Nhien N, Nakamori M, Nishikawa T, Yamamoto S, Ota F. Vitamin A deficiency in patients with diarrhea and HIV infection in Ethiopia. Asia Pac J Clin Nutr. 2007; 16(1):323-328.
57. Semba RD, Miotti PG, Chiphangwi JD, Saah AJ, Canner JK, Dallabetta GA, Hoover DR. Maternal vitamin A deficiency and mother-to-child transmission of HIV-1. Lancet 1994; 343:1593–1597.
58. Semba RD, Kumwenda N, Taha TE, Mtimavalye L, Broadhead R, Miotti PG, Eisinger W, Hoover D, Chiphangwi JD. Plasma and breast milk vitamin A as indicators of vitamin A status in pregnant women. Int J Vitam Nutr Res. 2000; 70:271–277.
59. Melikian G, Mmiro F, Ndugwa C, Perry R, Jackson JB, Garrett E, Tielsch J, Semba RD. Relation of vitamin A and carotenoid status to growth failure and mortality among Ugandan infants with human immunodeficiency virus. Nutr. 2001; 17:567–572.
60. Beach RS, Mantero-Atienza E, Shor-Posner G, Javier JJ, Szapocznik J, Morgan R, Sauberlich HE, Comwell PE,Eisdorfer C, Baum MK.. Specific nutrient abnormalities in asymptomatic HIV-1 infection. AIDS 1992; 6:701–708.
61. Papathakis PC, Rollins NC, Chantry CJ, Bennish ML,Brown KH. Micronutrient status during lactation in HIV-infected and HIV-uninfected South African women during the first 6 mo after delivery. Am J Clin Nutr 2007; 85:182–192.
62. Koch J, Neal EA, Schlott MJ, Garcia-Shelton YL, Chan MF, Weaver KE, Cello JP. Zinc levels and infections in hospitalized patients with AIDS. Nutr. 1996; 12:515–518.
63. Wellinghausen N, Kern WV, Jöchle W, Kern P. Zinc serum level in human immunodeficiency virus-infected patients in relation to immunological status. Biol Trace Elem Res. 2000; 73:139–149.
64. Dworkin BM, Rosenthal WS, Wormser GP, Weiss L. Selenium deficiency in the acquired immunodeficiency syndrome. JPEN J Parenter Enteral Nutr. 1986; 10:405–407.
65. Mantero-Atienza E, Beach RS, Gavancho MC, Morgan R, Shor-Posner G, Fordyce-Baum MK. Selenium status of HIV-1 infected individuals. JPEN J Parenter Enteral Nutr. 1991; 15:693–694.
66. Baum MK, Shor-Posner G, Lu Y, Rosner B, Sauberlich HE, Fletcher MA, Szapocznik J, Eisdorfer C, Buring JE, Hennekens CH. Micronutrients and HIV-1 disease progression. AIDS 1995; 9:1051–1056.
67. Graham NM, Sorensen D, Odaka N, Brookmeyer R, Chan D, Willett WC, Willett WC Morris JS, Saah AJ. Relationship of serum copper and zinc levels to HIV-1 seropositivity and progression to AIDS. J Acquir Immune Defic Syndr. 1991; 4:976–980.
68. Cirelli A, Ciardi M, de Simone C, Sorice F, Giordano R, Ciaralli L, Costantini S. Serum selenium concentration and disease progress in patients with HIV infection. Clin Biochem. 1991; 24:211–224.
69. Kupka R, Msamanga GI, Spiegelman D, Morris S, Mugusi F, Hunter DJ, Fawzi WW. Selenium status is associated with accelerated HIV disease progression among HIV-1-infected pregnant women in Tanzania. J Nutr. 2004; 134:2556–2560.
70. Campa A, Shor-Posner G, Indacochea F, Zhang G, Lai H, Asthana D, Scott GB, Baum MK. Mortality risk in selenium-deficient HIV-positive children. J Acquir Immune Defic Syndr Hum Retrovirol. 1999; 20:508-513.
71. Kupka R, Msamanga GI, Spiegelman D, Rifai N, Hunter DJ, Fawzi WW. Selenium levels in relation to morbidity and mortality among children born to HIV-infected mothers. Eur J Clin Nutr. 2005; 59:1250-1258.
72. Tapiero H, Townsend DM, Tew KD. Trace elements and pathology: copper. Biomed Pharmacother. 2003; 57(319): 13–17.
73. Galloway P, Donald CM, Naveed S. Effect of the inflammatory response on trace element and vitamin status. Ann Clin Biochem.2000; 37:289-297.
74. Zowczak M, Israel M, Tomlinson L, Cofta S. Analysis of serum copper and zinc concentrations in cancer patients. Biol Trace Elem Res. 2001; 82:1-8.
75. Guo J, Wu T, Anderson J, Kane BF, Johnson DG, Gorelick RJ, Henderson LE, Levin JG. Zinc finger structures in the human immunodeficiency virus type 1 nucleocapsid protein facilitate efficient minus-and plus-strand transfer. J Virol. 2000; 74:8980–8988.