Research Journal of Chemical and Environmental Sciences
Res J. Chem. Environ. Sci. Vol 8 [5] October 2020: 36-41
Online ISSN 2321-1040
CODEN: RJCEA2 [USA]

Website: www.aelsindia.com/rjces.htm

REVIEW ARTICLE

Micronutrients and their role in immunity

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ABSTRACT
The immune system's function is to shield the body from dangerous environmental stimuli including microorganisms. However, if the immune response is not adequate, it may have harmful implications, such as increased susceptibility to infections if immune function is poor, or allergies, autoimmune conditions, and chronic inflammation if immune function is high. Vitamins and minerals (micronutrients) play an important part in immune system control and forming. Inadequate amounts of micronutrients are related to reduce levels of natural killer, granulocyte, and phagocytic cell function, as well as T and B cell proliferation and trafficking, as well as enhanced susceptibility to inflammatory disorders, infection, and altered vaccine efficacy. This exploratory review elucidates the role of chromium, cobalt, zinc, iron and vitamins A, C and E as immunoregulator in different species.
Keywords- *micronutrients, immune system, vitamins, minerals*

Received 22.07.2020 Revised 24.08.2020 Accepted 19.10.2020

INTRODUCTION

Immunity refers to reactions by an animal's body to foreign substances such as microbes and various macromolecules, independent of a physiological or pathological result of the reaction [1]. The nutritional status, immune status and disease resistance of an animal are interlinked to each other. Adequate nutrition maintains animal health and provides disease resistance. Among the three type of immunity *viz.*, innate immunity, adaptive immunity and passive immunity, the only common factor that affects all the three is nutrition. "Immune nutrition" is a branch of science that deals with nutrients that help in prevention of diseases and regulate the immune system. Many micronutrients are considered to be responsible for immunomodulation of the animal. Micronutrients are bio elements which are required in minute quantity, but are essential for the proper functioning of the body. Minerals such as chromium, cobalt, zinc, iron and vitamins A, C and E are proven to be actively involved in immunoregulation in different species.

EFFECT OF SUPPLEMENTATION OF DIFFERENT MINERALS ON IMMUNE RESPONSE IN VARIOUS SPECIES:

Nagalakshmi *et al.* [24] supplemented 15 ppm Zn as proteinate and sulphate in lambs and obtained higher immune response compared to control animals. Among the two forms, organic form of Zn (proteinate) was more effective than inorganic form. Organic forms of minerals when supplemented in newly born calves improved total immunoglobulin levels in the colostrum [11, 16] and blood serum [16]
Chelated forms of Cu, Mn, and Zn were reported to enhance immune response of early lactation dairy cows [25]. Senthilkumar *et al.* [34] supplemented organic copper in lambs and consequently ceruloplasmin, erythrocytic super-oxide dismutase activity and cell mediated immune response were higher than control lambs. Higher antioxidant enzyme activities viz., superoxide dismutase, catalase and glutathione peroxidase are obtained in lambs by supplementation of Zn proteinate [24], combination of

Cu and Zn methionine in ewes [30], organic Se in lambs [17] and organic mineral combination (Fe, Cu, Zn and Mn) in chicks [33] than the inorganic mineral supplemented groups. Ohh and Lee [28] also observed that supplementation of organic Cr resulted in an improved recovery to normal status, growth performance, metabolic response and disease susceptibility in both animals and human beings stressed by either physical, physiological, environmental, pathological or nutritional reasons. Organic trace mineral supplementation tended to reduce the percentage of calves that received a second antibiotic treatment that were with stress from shipping and also had a greater antibody response to infectious bovine rhino-tracheitis virus vaccination [14]. Organic minerals also decreased mortality of newborn calves [11]. The role of individual micronutrients in immunity are described below.

Component	Location	Nutrient involved	Function
Ascorbic acid	Cytosol	Vitamin C	Reacts with several types of ROS/RNS
Alpha tocopherol	Membrane	Vitamin E	Break FA peroxidation chain reaction
β-Carotene	Membrane	β-Carotene	Prevents initiation of fatty acid peroxidation chain reactions
Superoxide dismutase (SOD)	Cytosol	Cu, Zn, Mn	An enzyme that converts super oxide to hydrogen peroxide
SOD	Mitochondria	Mg, Zn	converts superoxide to hydrogen peroxide
Glutathione peroxidase	Cytosol	Se	converts hydrogen peroxide to water
Catalase	Cytosol	Fe	converts hydrogen peroxide to water
Ceruloplasmin	water phase	Cu	An antioxidant protein, may prevent copper and iron from participating in oxidation reactions

MICRONUTRIENTS INVOLVED IN PREVENTION OF OXIDATIVE STRESS

Chromium

Chromium is an essential micro nutrient which helps in alleviation of stress in livestock, thus gaining worldwide popularity as "stress relieving factor" [23]. It can occur in various oxidation states from -2 to +6. Supplementation of chromium is generally done in two forms having high bioavailability *viz.,* trivalent Cr^{3+} and hexavalent Cr^{6+}. Trivalent chromium is needed for normal carbohydrate, lipid and protein metabolism. Chromium gets converted to biologically active chromium, which is a part of an insulin signaling pathway and affects carbohydrate and lipid metabolism via insulin. It also helps in improving insulin sensitivity [6]. Chromium also helps in alleviating heat stress in lactating cows [22]. Chromiumhelps in improvement of cellular and humoral immunity, and also decreases cortisol in stressed animals. It also prevents incidences of ketosis by enhancing insulin sensitivity. Insulin is an anabolic hormone which promotes lipogenesis and inhibits lipolysis. Chromium regulates glucose metabolism, which is the primary fuel for the body cells, fetal growth and milk production [12]. Chromium deficient animals, if supplemented with additional amount of chromium, increases glucose uptake by insulin-dependent organs like muscles and adipose tissue [39]. Supplementation of chromium in enhanced glucose uptake in adipose tissue, reduces lipolysis, allows faster rate of feed intake, hence increases milk production [20]. Chromium has a profound effect onimmune response and disease resistance in cattle, owing to its glucose sparing effect.

Cellular immunity: In a study by Burton *et al.* [4], lymphocytes from dairy cows supplemented with 0·5 mg Cr as a Cr–amino acid chelate/kg diet from 6 weeks prepartum to 16 weeks post-partum had increased blastogenic responses to mitogen (concavalin A) stimulation. The proliferative effect of dietary Cr on the growth of isolated peripheral lymphocytes in response to mitogen stimulation indicates its role in cellular immunity.

In another study by Chang *et al.* [5], somecalves were exposed to certain stressors and hence showed signs of morbidity, while others served as control. In calves exposed to stress, Cr supplementation as an amino acid chelate (0·14 mg/kg) increased Con A-induced lymphocyte blastogenesis, but not in calves with normal body temperatures and no visual signs of sickness

Humoral immunity: Humoral immunity is evaluated by measuring the production of specific antibodies after the administration of a foreign antigen or vaccine.Chromium supplementation favours cell mediated and humoral immune response. Burton *et al.* [4] supplemented dairy cows with 0·5 mg Cr/kg diet as an amino acid chelate and observed that the supplemented cows had greater primary and secondary antibody responses to ovalbumin than control cows.

Copper

Copper has an important role in the maintenance of immunocompetence. Copper deficiency results in decreased humoral and cell-mediated, as well as nonspecific immune function. Impairment of immune function may be highly correlated with an increased incidence of infection and higher mortality rates observed in copper-deficient animals. The actual mechanisms by which copper is involved in immune processes are not well defined.

Phagocytosis and killing of infectious microorganisms are important functions of nonspecific cellular immune effectors such as macrophage, monocytes, and neutrophils. Newberne et al. [26] were able to demonstrate the importance of the reticuloendothelial system (RES) in copper-deficient rats infected with *Salmonella typhimurium*.

Copper is a component of enzymes such as cytochrome oxidase, necessary for electron transport during aerobic respiration. It is also an integral component of superoxide dismutase, which protects cells from the toxic effects of oxygen metabolites, particularly important to phagocytic cell function [27].

Copper is an essential trace mineral and is a major contributor to the functioning of Superoxide dismutase-I also called as Cu/Zn SOD, as it consists of both copper and zinc [31, 40]. Superoxide dismutase is an antioxidant enzyme possessing the property to scavenge free radicals, which can be detrimental to biological membranes by attacking its bilipid component.

Cobalt

A dietary concentration of 0.1 mg/ cobalt/kg DM is needed to maintain rumen function [15]. Microorganisms in the rumen require dietary cobalt for the synthesis of vitamin B_{12}, which is involved in the activity of two intermediates involved in regulation of cyanocobalamine activity, *viz* .,methylmalonyl CoA mutase and methionine [15]. Dietary insufficiency of cobalt in ruminants gives rise to vitamin B_{12} deficiency, which in sheep is characterised by illthrift, loss of weight, serous ocular discharge and acute photosensitisation [41]. Cobalt disrupts the immune function in small and large ruminants, leading to increased susceptibility to infection in ewes, for the viability of newborn lambs [9]. It also leads to stillbirth and perinatal mortality in lambs, due to decreased immune action [10], which makes cobalt an important trace mineral involved in immunity.

Zinc

Zinc is essential for the proper functioning of cell-mediating innate immunity, neutrophils, and natural killer cells. Macrophages, phagocytosis, intracellular killing and cytokines production are all affected by zinc deficiency. It also affects the secretion and functions of cytokines, which are the basic transmitting messengers of the immune system. The growth and function of T and B cells are also affected adversely due to zinc deficiency [32]. Apoptosis is induced by zinc deficiency. Zinc functions as an antioxidant and stabilizes membranes. It is important for maintenance and development of immune cells of both the innate and adaptive immune system. Imbalanced zinc homeostasis affects immune cells, hampering the formation, activation, and maturation of lymphocytes, low cytokine activity and weakened innate host defense by phagocytosis [18]. Zinc is an active participant in both cell mediated and humoral immunity. During the acute phase of an infection, the concentrations of trace elements like zinc decreases in the plasma. This occurs due to a systemic response by the cytokines. Leucocytes and pathogens critically depend on zinc [36]. Thus, cellular immunity is affected by the concentration of zinc in the vicinity of cytokines.

Concerning humoral immunity, B-cells play an essential role in the humoral immune response by producing antibodies [13]. B cell count decreases during zinc deprivation due to the impairment of lymphopoiesis [7].

In zinc-deficient conditions, a reduced immune response to vaccination *in vivo* was reported by many researchers [43] which suggest a possible enhancement of antibody formation by zinc supplementation.

Vitamin A

β-Carotene is the major precursor of vitamin A that is present naturally in green fodder. It may affect immune function, independent of its role as a source of vitamin A. β-Carotene *per se* can serve as an important antioxidant, which is not the case in vitamin A. Vitamin A-deficient animals are more prone to infections. Cows supplemented with β-carotene around dry-off had lower rates of new mammary gland infections during early dry-off. β-carotene and vitamin A prevent ROP and metritis in dairy cows [37]. The addition of low concentrations of β-carotene to bovine lymphocyte cultures also stimulated mitogen-induced blastogenesis.

Folic acid

The status of folic acid plays a major role in the immune system.Mononuclear cells play a key role in the development of vascular diseases by integrating to injured endothelium after vascular injury and supporting tissue remodelling.Natural killer cells are lymphocytes, inherent to the immune system. Folic acid is essential for the proliferation of these natural killer cells [21]. Folate deficiencies can lead to increased susceptibility to infection by decreasing the number of circulating T cells which respond to mitogenic activation.

Cyanocobalamine

Vit.B_{12} play a central role in immune processes because it governs cell division and growth. B12 deficiency causes immune cell dysfunction by a reduction in CD8+ and natural killer (NK) cells and increased production of tumour necrosis factor alpha (TNF-α) and interleukin (IL)-6 by macrophages [39]. The maturation of leucocytes does not take place in the deficiency of vitamin B_{12}. The deficiency also decreases WBC response and hypotrophy of thepivotal immune system organ, thymus. Vitamin B_{12} deficiency has been also involved in increased susceptibility to infections [19].

Cobalt deficiency disrupts neutrophil function and resistance to parasitic infection.Vitamin B12 deficiency can also impair the function of monocytes.

Vitamin E

Vitamin E, primarily a-tocopherol, is the scavenger of peroxyl radical in biological lipids, like membranes or LDL (low-density lipoprotein). It is involved in cellular antioxidant metabolism. The antioxidant action of vitamin E is due to its ability to act as a free radical chain-breaking molecule. This chain-breaking property makes vitamin E different from other antioxidants. Vitamin E decreases inflammatory mediator production through cell signaling and gene expression, reducing the production of pro-oxidants, and promoting gut barrier function. Dietary vitamin E and C deficiency decreases erythrocyte GPx activity. Vitamin E inhibits lipid peroxidation, and thus protects the immune system [3]. The role of vitamin E as an antioxidant ascertains its importance in immune responses. Vitamin E functions as an essential component of the enzyme GSH peroxidase, which destroys peroxide and lipid hydroperoxides. Although Se and vitamin E function independently, they are synergistic in their roles in immune function. Humoral immune responses are shown to be enhanced by increasing dietary Se and/or vitamin E. The formation of free radicals in the lipid part of cell membranes can cause a dangerous chain reaction that damages the integrity of the membrane and can cause cell death.Vitamin E is stored in the lipid portion of cell membranes. By supplying an electron to free radicals, it protects the lipid molecules in our cell membranes from being oxidized and stops the chain reaction of oxidative damage [42].

Vitamin C

Vitamin C (ascorbic acid) is a low molecular weight antioxidant. It circulates freely in plasma, leukocytes, and red blood cells and enters into all tissues and body fluids. Vitamin C is actively transported into blood leukocytes, thereby up keeping a high vitamin C concentration. Vitamin C prevents peroxidation of membranephospholipids and acts as a scavenger of free radicals in the brain, and is required for the synthesis of several hormones and neurotransmitters. Vitamin C, is a readily available antioxidant, and does not induce the complication of renal dysfunction [3]. Several reports indicate that during infections and stress, vitamin C concentrations in the plasma decreases sharply and supplementation of vitamin C boosts the function of the human immune system, such as antimicrobial and natural killer cell activities, lymphocyte proliferation, chemotaxis, and delayed-type hypersensitivity. Additionally, vitamin C contributes to maintaining the redox integrity of cells andshields them against reactive oxygen species generated during the inflammatory response, therefore, adequate intake of vitamin C ameliorates symptoms and shortens the duration of respiratory tract infection [29]. In addition, it is found that vitamin C, vitamin E, and beta carotene, play an important role in cellular radioprotection. Vitamin C is a carrier of electrons and functions as an antioxidant; it can also donate electrons to highly reactive free radicals such as hydroxyl and superoxide radicals and quench their free valency. Vitamin C stimulates liver detoxifying enzymes and helps the body to fight against pollutants. Supplementation of vitamin C improves important components of the immune system such as antimicrobial and natural killer (NK) cells, lymphocytes, chemotaxis activity and delayed-type hypersensitivity. Vitamin C is present in higher concentration in in phagocytes and lymphocytes than in plasma. Vitamin C assists in wound healing and prevents spread of infections [8].

Biological effects of Vitamin C:

- It is required for collagen synthesis
- It helps to maintain skin and epithelial tissue
- Neutrophils and plasma contain high vitamin C concentration
- Stimulates motility and phagocytic capacity of neutrophils
- Plays a key role in acute disease, infection corticosteroid administration, and trauma
- Protects neutrophils from oxidative damage
- It promotes phagocytosis and killing of bacteria inside neutrophils
- It stimulates interferon production

- It reduces the suppressor activity of mononuclear leukocytes
- Low blood vitamin C level may compromise the resistance against infectious diseases. It helps against infertility [35].

Role of vitamin C in body defense mechanisms:

- In skin and mucous barriers: Vitamin C piques collagen synthesis and strengthens skin barriers.
- In neutrophils and macrophages: Vitamin C stimulates the motility and chemotaxis of macrophages. It also enhances the killing of foreign bacterial cells (phagocytosis).
- Cellular and humoral immunity: Vitamin C strengthens humoral and cell-mediated immunity by proliferation of B cells and T cells respectively.
- Vitamin C also boosts the production of interferons, which act locally to fight against foreign bodies.

CONCLUSIONS

Oxidative stress occurs when production of free radicals exceeds the capacity of the antioxidant system of body cells. Stress conditions that give rise to free radicals can be classified as nutritional, environmental, and diseases. Certain nutrients serve as antioxidants or are components of antioxidant enzymes. Antioxidants include vitamins C and E, carotenoids, and antioxidant enzymes containing Se, Cu, Mn, Fe or Zn. Antioxidant nutrients play important roles in animal health by inactivating harmful free radicals produced through normal cellular activity and from various stressors. Vitamins and trace elements, in particular, are necessary for the synthesis of immune defense components (including immunoglobulins, cytokines and enzymes). Thanks to their antioxidant and/or anti-inflammatory properties they ascertain optimum functionality or regulate immune cell processes.

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CITE THIS ARTICLE

R. Srivastava, P. Singh, M. S. Rajput, G. Kumar and D. K. Yadav.Micronutrients and their role in immunity. Res. J. Chem. Env. Sci. Vol 8 [5] October 2020. 36-41