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Biological function of Nickel and its interaction with other minerals in cattles: A review

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Abstract
Nickel (Ni) is a silvery-white, hard, ductile metal existing in oxidation states; in biological systems, Ni2+ is the prevalent form. Dietary supplements of Nickel (Ni) can result in an increase in rumen urease activity and can increase growth rate and food conversion efficiency in cattles. Ni may also play role to stimulate or inhibit the release of various hormones. Ni activates certain enzymes related to the breakdown or utilization of carbohydrate, protein and lipid. Ni can induce various effects on the immune system, depending on dose, physicochemical form of the compound and route of exposure.

Keywords: Nickel, Cattles, hormones, enzymes, immunity

Introduction
Trace elements, also called trace metals, are present in small amounts as constituents of all living organisms and despite the minuscule level of their presence, are vital for the growth, development and general well-being of those organisms. It plays a crucial role in many biochemical processes, mainly as components of vitamins and enzymes (Bartzokis *et al.*, 2007; Zecca *et al*. 2004) [6, 74]. Trace elements are present in every biological process, from the production of energy and hormones, associate with some protein, nerve transmission, cholesterol and blood sugar levels, and muscle contraction to the regulation of pH, digestion, metabolism and others (Qureshi *et al*. 2005) [48].
Nickel (Ni) is a silvery-white, hard, ductile metal existing in oxidation states; in biological systems, Ni2+ is the prevalent form. Nickel (Ni) is both essential and toxic in the body. Nickel helps in iron absorption, improves bone strength, as well as glucose and adrenaline metabolism, hormones, lipid, cell membrane, and may also play a role in production of red blood cells (Wilfred, 2012) [71, 72]. When nickel enters the body, it is distributed to all organs, but mostly in the lungs, kidney and bone (Samal and Mishra, 2011) [51, 52]. Urinary excretion is the major route for the elimination of absorbed nickel (Mudjari and Achmad, 2018) [36]. Nickel may affect rumen microbial fermentation in ruminants, as Ni is a component of bacterial urease and cofactor F430 in methanogenic bacteria. There is little evidence that dietary Ni limits animal production under practical conditions (Spears, 2019) [66].
Hence, the literature pertaining to the supplementation of Ni in growing cattle has been reviewed under following subheadings:

1. Biological functions of nickel
   - 1.1 Role of nickel in nutrient metabolism
   - 1.2 Effect of nickel on blood metabolites
   - 1.3 Role of nickel in enzymatic activity
   - 1.4 Role of nickel in hormonal activity
   - 1.5 Role of nickel in antioxidant status
   - 1.6 Role of nickel in immunity
2. Interaction with other minerals

Biological functions of nickel
Although Ni is generally evenly distributed in the body but their biological role is not yet fully known.

Role of nickel in nutrient metabolism
Ni activates certain enzymes related to the breakdown or utilization of carbohydrate, protein and lipid. Ni deprivation resulted in lowered activities of a number of liver enzymes as well as

decreased concentrations of triglycerides, glucose and glycogen in liver and decreased concentrations of urea, ATP and glucose in serum (Schnegg and Kirchgessner, 1979) [54] [Ni aids in Fe absorption, as well as adrenaline and glucose metabolism, hormones, lipid, cell membrane, improves bone strength and may also play a role in production of red blood cells (Wilfred, 2012; Peter, 2015) [71, 72, 46]. Ni is present in RNA and DNA where it functions is associated with the stabilizing RNA structure (Petzold and Al-Hashimi, 2011) [47]. Ni has been shown to bind both the phosphates and heterocyclic bases of DNA and RNA and stabilizes RNA and DNA against denaturation (Shi *et al*., 1972) [56]. A Ni-metalloprotein named "Nioplasmin" has been isolated from human and rabbit serum (Sunderman *et al*., 1972a) [62]. Nomoto (1980) [45] found 43% of the total serum Ni in humans in the fo rm of Nioplasmin. Unfortunately, there is no clear indication of the physiological significance or function of Nioplasmin. Clary (1975) [10] and Horak and Sunderman (1975) [21] [observed that Ni-induced hyperglycemia is antagonized by exogenous insulin, and Horak and Sunderman (1975) [21] reported that the hyperglycemic response to Ni is suppressed but not completely prevented by adrenalectomy or hypophysectomy. The marked reduction in hepatic fructose-2, 6-bisphosphate (an indicator of gluconeogenic /glycolytic state) a short time after Ni injection suggested that mainly gluconeogenesis and not glycogenolysis contributes to the enhanced plasma glucose. Ni induced rise of blood glucose level could be due to involvement of nitric oxide-mediated pathways (Gupta *et al*., 2000) [19]. Ni causes an increase in the level of cGMP and constitutive nitric oxide synthase (c-NOS) in the adrenals and brain or inducible nitric oxide synthase (i-NOS) in the pancreas by modulating the release of insulin from pancreas finally leading to hyperglycemic condition.

Effect of nickel on blood metabolites

Ni deficiency in the rat resulted in decreased hematocrit, hemoglobin concentrations and erythrocyte counts (Schnegg and Kirchgessner, 1978) [53]. Nielsen and Sauberlich (1970) [38] found that feeding chicks a diet containing 2 to 15 ppb Ni for upto 4 weeks resulted in: (1) ultrastructural changes in the liver; (2) decreased O_2 consumption by liver homogenates; (3) decreased liver phospholipid; (4) reduced hematocrit; (5) decreased plasma cholesterol as compared with birds receiving 3 ppm supplemental Ni. Effect of dietary Ni on plasma alkaline phosphatase is highly dependent on the Fe and Cu status of the animal (Nielsen and Zimmerman, 1981) [40]. High level of Ni supplementation reduced serum alkaline phosphatase activity in pigs (Spears, 1984) [65]. Serum alkaline phosphatase was lower at 49 days in pig given 25 ppm Ni compared to pigs receiving 5 ppm Ni (Spears, 1984) [65]. Whanger (1973) [70] found that 500 ppm Ni decreased plasma and liver alkaline phosphatase in the rat. Of the individual serum proteins, albumin, α-2 and γ globulins were decreased by Ni deficiency, while α-1 and β globulins were not affected when lambs fed the Ni deficient diet (Spears *et al*., 1978a) [59]. Serum urea nitrogen concentrations decreases with Ni supplementation in animals receiving the low protein diet, while gains tended to be greater for lambs and steers fed the Ni supplemented diets. The decrease in serum urea nitrogen coupled with the increased gain suggests that the higher urease activity in the Ni supplemented animals influences the recycling of nitrogen to the rumen. Ni deprivation results in lowered activities of a number of liver enzymes as well as decreased concentrations of triglycerides, glucose and glycogen in liver and decreased concentrations of urea, ATP and glucose in serum (Schnegg and Kirchgessner, 1978) [53]. In long-term study, Anke *et al*. (1977) [3] found that goats supplemented with diet containing 0.1 ppm Ni gains at 21% slower than animals fed the basal di*et al*.ong with with 10 ppm Ni. Ni deficiency in goats also resulted in (1) increased mortality in young goats and lactating goats; (2) decreased hematocrit and hemoglobin concentrations in lactating goats; (3) decreased bone and liver Zn; (4) lowered serum glutamate AST activity (Anke *et al*., 1977, 1980b) [3, 4, 5]. Triacylglycerol accumulation in liver, with more concentrations of saturated fatty acids and polyunsaturated fatty acids in Ni deficit animals (Samal and Mishra, 2011) [51, 52].

Role of nickel in enzymatic activity

A number of enzymes have been activated or inhibited by Ni (Nielsen, 1971) [43]. Ni can replace the natural occurring metals in the metalloenzymes carboxypeptidase and phosphoglucomutase and the resulting activities have been found to be similar in both cases to the natural metalloenzyme (Coleman and Vallee, 1961; Ray and Multani, 1972) [11, 49]. However, no mammalian enzyme has been found to require Ni as an intrinsic component. Various Ni containing enzymes are urease from several plants like jack beans and microorganisms, Ni-Fe hydrogenase, carbon monoxide dehydrogenase from acetogenic bacteria, acetyl-CoA decarbonilase/synthase, methyl coenzyme M reductase, certain superoxide dismutases, some glyoxylases, acireductone dioxygenase (ARD), and methylene diurease. Ni deficient animal shows lower activities of the lipogenic enzymes glucose-6-phosphate dehydrogenase, 6-phosphogluconate dehydrogenase, malie enzyme and fatty acid synthase (Samal and Mishra, 2011) [51, 52]. Ni-Fe-Hydrogenase is a type of hydrogenase, which is an oxidative enzyme that reversibly activates molecular hydrogen (Lubitz, 2007) [32]. The catalytic site on the enzyme provides hydrogen-metabolizing microorganisms a redox mechanism by which to store and utilize energy.

Ureases are the Ni containing metalloenzymes of high molecular weight (Krajewska, 2012) [28]. They functionally, belong to the superfamily of amidohydrolases and phosphotriesterases. Urease catalyzes the hydrolysis of urea into carbon dioxide and ammonia. Ureases are found in numerous bacteria, fungi, algae, plants and some invertebrates, as well as in soils. Urease hydrolyzes feed urea to a form of nitrogen that can be used by most rumen microorganisms and also hydrolyzes endogenous urea that is recycled to the rumen via saliva and by transfer across the rumen wall (Somers, 1961) [57]. Urease present in rumen epithelial tissue greatly facilitates the transfer of urea-nitrogen from the blood across the rumen wall (Houpt, 1970) [22]. Supplementation of diets containing 0.26 to 0.85 mg Ni/kg DM have increased ruminal urease, growth rate and feed conversion efficiency of lambs (Spears *et al*., 1986) [58]. The largest responses to Ni supplementation have occurred in ruminants fed high concentrate and low protein diets (Spears *et al*., 1979) [60]. These findings suggested that Ni may function, when dietary nitrogen (N) intake is low, to enhance the recycling of N to the rumen by increasing ruminal epithelium urease activity (Spears and Hatfield, 1980) [63].

Role of nickel in hormonal activity

Ni may also play role to stimulate or inhibit the release of

various hormones. At low concentrations, Ni specifically inhibited prolactin release from the pituitary but at higher concentrations, stimulates release of growth hormone, thyrotropin, luteinizing, follicle-stimulating and adrenocorticotropic hormones from bovine pituitary (La Bella *et al*., 1973a & b) [29, 30]. Dormer *et al*. (1973) [16] reported that Ni inhibit growth hormone release from the bovine pituitary gland and insulin release from the pancreas. Ni possesses an insulin-like activity on fat-cell membranes in rats, with stimulation of glucose incorporation and diminution of lipolysis. Ni-induced hyperglycemia could be due to an increased pancreatic release of glucagons. Clary (1975) [10] noted progressive diminutions in concentrations of plasma insulin following intratracheal administration of $NiCl_2$. The Ni induced hypoinsulinemic response was attributed to modulating insulin secretion by stimulating α-2 adrenergic receptors in pancreatic islets (Alverez *et al*., 1993) [1]. Such alterations were found to lead to a drastic drop in the insulin/glucagon plasma ratio (Cartana and Arola, 1992) [8]. Intra-peritoneal injections of Ni in the rat shows increase plasma glucagon (Horak and Sunderman, 1975) [21] and decrease insulin (Clary, 1975) [10]. Inhibition of insulin release could be related to the extremely high concentration of Ni found in the pituitary and the effect of Ni on the secretion of the pituitary hormones. Dietary Ni affected the response of chicks to thyroid hormone and epinephrine (Nielsen, 1972) [44]. Feeding of Ni deficient diet (13µg/kg diet) or a Ni adequate diet (1mg/kg) to rats indicated that Ni deficiency significantly lowered the concentration of T_3 and T_4 hormones. Ni nanoparticles increases follicle stimulating hormone (FSH) and luteinizing hormone (LH), and decreases etradiol (E_2) serum levels at a dose of 15 and 45 mg/kg in female rats. Ovarian lymphocytosis, vascular dilatation and congestion, inflammatory cell infiltration, and increase in apoptotic cells are reported in ovary tissues in exposure groups.

Role of nickel in antioxidant status

Suitable mechanisms are present in body so that steady state concentration of potentially toxic oxygen derived free radicals is kept in check under normal physiological condition by body's intrinsic antioxidant defense system. But enhanced generation of these reactive oxygen species (ROS) can overwhelm cell's intrinsic antioxidant defenses and result in oxidative stress (Valko *et al*., 2006) [69]. SOD, catalase (CAT) and glutathione peroxidase (GSH-Px) are the important enzymes and antioxidant molecule in the antioxidant system against oxidative stress (Fang *et al*., 2002) [17]. Ni-SOD is a metalloenzyme that protects cells from oxidative damage by catalyzing the cytotoxic O_2^- to H_2O_2 and molecular oxygen (Jason, 2014) [24]. Ni compounds adversely affect cells by modulating ascorbic acid metabolism and other metabolic pathways (Das *et al*., 2001) [14]. Ni may bind to DNA repair enzymes and generate oxygen free radicals to cause protein degradation. This irreversible damage to the proteins involved in DNA repair, replication, recombination, and transcription could be important for the toxic effects of Ni (Lynn *et al*., 1998) [33]. Peritoneal administration of Ni choloride to rats enhances lipid peroxidation in the liver (Donskoy *et al*., 1986) [15]. Stinson *et al*. (1992) also reported Ni chloride induces hepatic lipid peroxdation under *in vitro* and *in vivo* conditions. Ni sulfate also induces lipid peroxidation in liver and kidney of male rats (Das *et al*., 2001) [14]. Misra *et al*. (1990) [35] noted that high level of lipid peroxidation in vital organs, which may result in increased concentration of H_2O_2. Ni is known to inhibit of H_2O_2 scavenging enzymes like catalase, thus two effects combined could augment the potential of oxidative cell damage in cells (Rodriuge and Kasprzak, 1989) [50]. An emerging mechanism evolved in the transformation of Ni^{+2} to Ni^{+3} by various intracellular oxidants such as hydrogen peroxide, which may occur subsequent to the binding of Ni ions to certain ligands. This oxidation may result in the formation of oxygen radicals (Salnikow *et al*., 1994) [37]. The production of oxygen radical may lead to DNA strand breaks (Chen *et al*., 1998) [9]. Glutathione (GSH) is known to provide major protection against xenobiotics. Depletion of GSH below a critical concentration allows an enhancement of lipid peroxidation evoked by endogenous substances. This could result in oxidative stress leading to induction of ROS that play a key role in damaging DNA (Danadevi *et al*., 2004) [13]. It has been reported that ROS and binding of Ni to proteins are involved in Ni inhibition of DNA repair. It is conceivable that Ni also binds to many cellular proteins, particularly those rich in histidine residues, and generates oxygen free radicals, to cause protein damage in situ. Irreversible damage to the proteins involved in DNA replication, repair, recombination, and transcription are crucial for the toxic effects of Ni (Lynn *et al*., 1997).

Ni induced activation of hypoxia inducible factor-1 (HIF-1) and the upregulation of hypoxia inducible genes are due to depleted intracellular ascorbate levels. The strongest epigenetic effects on Ni have been associated with HIF-1. The HIF-1 transcription factor is involved in the regulation of hypoxia inducible genes involved in cell transformation, tumor promotion, and progression, angiogenesis, altered metabolism, and apoptosis. HIF- la, one of the HIF-1 subunits, is over-expressed in both primary and metastatic tumors. It is induced in response to hypoxia and exposure to nickel (Li *et al*., 2004) [31]. Both soluble and insoluble Ni compounds have also been shown to induce Cap43 (also called NDRG2) gene expression, which requires HIF- la activation (Costa *et al*., 2002) [12].

Role of nickel in immunity

Ni exhibits both immunomodulatory and immunotoxic effects (Kimber and Dearman, 1994) [26]. Ni can induce various effects on the immune system, depending on dose, physicochemical form of the compound and route of exposure. Workers exposed to Ni shows significant increases in levels of IgG, IgA, and IgM and a significant decrease in IgE levels (Bencko *et al*., 1983) [7]. Significant increases in other serum proteins, which may be involved in cell mediated immunity (including α1-antitrypsin, α2-macroglobulin, and ceruloplasmin), were also noticed by Bencko *et al*. (1983) [7]. Ni significantly depressed the circulating antibody response of rats immunized with a viral antigen, with the greatest decrease in antibody titers noted in animals receiving the metal two weeks before the initial antigen dose (Graham *et al*., 1975) [18]. Ni salts ($NiCl_2$ and $NiSO_4$) can induce immunosuppression in mice and that Ni salts affect the T-cell system and suppress the activity of natural killer cells. Mitogen dependent lymphocyte stimulation was inhibited and in spleens of Ni supplemented mice. Exposure to Ni can cause an adverse impact in positive T cell percentage, cell proliferation and activation, and cytokine and antibody production, which may finally induce immunosuppression in the body (Graham *et al*., 1975) [18]. Cytokines, mainly from T-cells or macrophages, can not only impact the development

and differentiation of immunocytes but also have internal interaction with IL-2, IL-6, IL-10, IL-12, TNF-α/ LITAF, and IFN-γ mRNA expression, protein levels and IgA, IgG, and IgM contents. T subset percentages, and IgA+ B cell numbers are significantly decreased in the 300, 600, and 900 mg/kg $NiCl_2$ groups when compared with those of the control group, which shows that dietary $NiCl_2$ in excess of 300 mg/kg causes damage on splenocytes and immune function (Wu *et al*., 2013) [73]. Ni supplementation may contribute to the progression of target organ and/or inflammatory character, such as diabetes and myocarditis (Iiback *et al*., 1994) [23]. Ni is a strong biological sensitizer and may induce a delayed type hypersensitivity reaction (type IV immune response). The immunosuppressive effects of Ni are found to be transient with responses returning to normal within a few days (Menne, 1996) [34].

Interaction of nickel with other minerals

Ni has been reported to interact or influence the metabolism of a number of other elements. It has been suggested that many effects of Ni are due to the interference with the metabolism of essential metals like Fe, Mn, Ca, Zn, or Mg (Kasprzak *et al*., 2003) [24]. The interrelationship between Fe and Ni has been studied extensively in the rat. Schnegg and Kirchgessner (1975b) reported that Ni deficiency in rats fed a diet containing 50 ppm Fe resulted in decreased erythrocyte counts, hematocrit and hemoglobin concentrations. Interaction between Fe and Ni in the rat was affected by form and level of dietary Fe (Nielsen, 1980c) [41]. Ni deficiency decreased hematocrit and whole body retention of an oral dose of ^{59}Fe only when Fe was provided in the ferric form at a slightly deficient level (Nielsen, 1980c) [41]. Ni and Fe interact both synergistically and antagonistically. In the synergistic relationship, Ni apparently enhanced or was required for Fe absorption (Nielson, 1979) [42]. The antagonistic or competitive relationship demonstrated that Fe deficiency apparently was more detrimental to Ni-supplemented than to Ni deficient rats; growth was more severely depressed and perinatal mortality was higher in supplemented rats (Nielson *et al*., 1979) [42]. Ni deficiency has decreased tissue Zn concentrations in goats (Anke *et al*., 1980b) [4, 5], lambs (Spears *et al*., 1978a) [59] and pigs (Anke *et al*., 1974) [2]. Ni partially alleviated some signs of Zn deficiency including depressed leukocyte counts, and elevated hematocrits, hemoglobin concentrations and erythrocyte counts. Zn was found to depress Ni absorption in chicks, but high levels of Ni had no effect on Zn absorption (Hill, 1977) [20]. Ni and Cu are also interrelated. Ni and Cu have similar physical and chemical properties, the interactions between those two elements may be result of isomorphous replacement of Cu by Ni at various functional sites that interfered with some biological processes. Spears *et al*. (1977a) [61] reported that Ni supplementation increased growth, hematocrit and hemoglobin level, but tended to reduce tissue Cu concentration in rats fed a Cu-deficient diet. Continued supplementation of Ni for longer periods of time was found to exacerbate Cu deficiency symptoms. Nielsen and Zimmerman (1981) [40] reported that Cu and Ni interacted antagonistically and that the interaction was influenced by level of dietary Fe. The findings showed that if Cu deprivation was not too severe, signs of Cu deficiency in rats were more severe with, than without, supplemental Ni (diet contained 16-20 ng/g), and that effect was greater when dietary Ni was 50 µg/g rather than 5 µg/g. Schroeder *et al*. (1974) [55] reported that dietary Ni supplementation decreased lung and spleen Cu. Spears *et al*. (1977) [64] found that supplementing Ni (20 µg/g of diet) to rats alleviated Cu deficiency signs of growth retardation. They speculated that Ni substituted for Cu at certain biological sites, thus sparing Cu for some vital functions. This speculation was supported by the finding that Ni tended to decrease the Cu content in some tissues of Cu deficient rats. Evidence for a noncompetitive interaction between Ni and Cu includes findings that Ni deprivation depressed the Cu level in liver, spleen, and kidney of rats (Schnegg and Kirchgessner, 1978) [53] and in liver of sheep (Spears *et al*., 1978) [62].

Conclusion

Dietary supplementation of nickel exerts positive effect on dry matter intake, feed intake and growth performance, Ni supplementation affects antioxidant status and immune response. It affects urease activity thus increase protein utilization. In this context, the study of effects of nickel on nutrition utilization and growth performance has become an upcoming aspect of nutritional research.

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